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ESTABLISHED 1820

HEMOGLOBIN CONSTRUCTION WITHIN THE BODY AS INFLUENCED BY DIET FACTORS. A CONSIDERATION OF ANEMIA PROBLEMS. By G. H. WHIPPLE, M.D. . . . 721

OPHTHALMOPLEGIA IN GRAVES' DISEASE. By A. M. WEDD, M.D. and H. H. PERMAR, M.D. 733

HYPERTHYROIDISM AND DIABETES. By HENRY J. JOHN, M.D. 741

TRANSIENT INSULIN HYPOGLYCEMIC HEMIPLEGIAS. By J. M. RAVID, M.D. 756

SUPRARENAL INSUFFICIENCY: REPORT OF TWO CASES. By HAROLD E. MARSH, M.D. 769

THE BLOOD PRESSURE IN PERNICIOUS ANEMIA. By J. LERMAN, M.D. and J. H. MEANS, M.D. 777

POLLEN ALLERGY. SKIN REACTIONS OF PATIENT BEFORE AND AFTER TREATMENT WITH SPRING (GRASS) POLLENS. By ROBERT W. LAMSON, PH.D., M.D., GEORGE PINESS, M.D., and HYMAN MILLER, M.D. 791

POLLEN ALLERGY. IV. WITH SPECIAL REFERENCE TO SKIN REACTIONS BEFORE AND AFTER TREATMENT WITH FALL POLLENS. By R. W. LAMSON, PH.D., M.D., GEORGE PINESS, M.D. and HYMAN MILLER, M.D. 799

TWO CASES OF PERIPHERAL NEURONITIS RESEMBLING LANDRY'S PARALYSIS. By ROSS H. THOMPSON, M.D. 807

FACIAL DIPLEGIA. By FRED P. CURRIER, M.D. 811

MERALGIA PARESTHETICA. By JAMES H. HUDDLESON, M.D. 823

A FLEXIBLE GASTROSCOPE. By WILLIAM S. COLLENS, M.D., and IRVING GRAY, M.D. . 831

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 42

Contents continued on page x

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1928

ORIGINAL ARTICLES.

HEMOGLOBIN CONSTRUCTION WITHIN THE BODY AS INFLUENCED BY DIET FACTORS.*

A Consideration of Anemia Problems.

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To most persons the term *hemoglobin* applies solely to the red coloring matter of the blood. It is probable that blood hemoglobin in reality is most important, but we should not lose sight of a very important red pigment—muscle hemoglobin, which in mammals forms an important part of striated muscle tissue. We propose to direct our attention toward this red muscle pigment, which can be isolated from striated muscle tissue and tested chemically and in the living animal.

Muscle Hemoglobin. One reason for the lack of study of muscle hemoglobin is the real difficulty of preparation, whereas by contrast it is very easy to prepare and study blood hemoglobin. Recently[7] we have published a method by which a solution of muscle hemoglobin can be prepared which is practically free from blood hemoglobin. In fact by delicate precipitin tests it has been shown[1] that a specific serum for dog-blood hemoglobin capable of giving a reaction in hemoglobin dilutions of 1 to 40,000 gave no evidence of the presence of blood hemoglobin in various samples of dog muscle hemoglobin carefully prepared by our method.

* Presented at the Nashville meetings of the American Association for the Advancement of Science, Section of Medical Sciences, December 28, 1927.

We have biologic evidence, therefore, that muscle hemoglobin and blood hemoglobin of the dog are distinct substances although they are almost indistinguishable by modern chemical methods. Even the absorption curves[2] plotted by means of the spectrophotometer are almost identical. When the muscle is given intravenously into the normal or anemic dog we find again slight but distinct biologic differences. *Blood hemoglobin* under these circumstances may be broken down to bile pigment and other end products for elimination but usually more or less is conserved for future construction into new hemoglobin. In severe anemia almost all of the injected blood hemoglobin (see Table V) may be conserved and rebuilt into new red cell hemoglobin.[11] Measured in the same manner *muscle hemoglobin* is somewhat different. When given intravenously to a dog it may be in large part broken down into bile pigment and other end products but probably there is some conservation too. In anemic dogs there is some evidence[11] that the injected *muscle hemoglobin* may be stored away in the body and in part reconstructed into *new blood hemoglobin*. Moreover the threshold of elimination for the kidney is much higher for blood hemoglobin than for muscle hemoglobin given intravenously in the dog.

It is well known that skeletal muscle may show gross differences in color, for example, veal is pale as compared with the deep-red color of beef muscle. This difference in color is not due to blood but almost wholly to large differences in the content of muscle hemoglobin. As a rule the young animal shows muscles which contain much less muscle hemoglobin than active adults. We have studied[7] these differences in pups and dogs of various types. One finds lowest values in young pups during the first month of life, when the values may average about 100 mg. per 100 gm. muscle. As the pups grow we see a gradual slow increase in muscle hemoglobin content in the striated leg and trunk muscles. At puberty the average for a lively young dog may be 400 to 500 mg. muscle hemoglobin per 100 gm. muscle. When the adult dog is very active and vigorous we observe the maximum values for skeletal muscle of about 1000 mg. muscle hemoglobin per 100 gm. muscle. This is usually observed in trained hunting dogs. When the dog is quiet and inactive, as a house dog, we may see values as low as 300 to 400 mg. muscle hemoglobin per 100 gm. muscle.

The *heart* shows a much more uniform muscle hemoglobin content, just as its work is more constant and uniform. A minimum of 100 to 200 mg. muscle hemoglobin per 100 gm. muscle is found in pups and an adult average of 300 to 400 mg. muscle hemoglobin. With severe training, as in a hunting dog, or associated with high blood pressure in chronic nephritis, we may observe maximal figures of about 700 mg. muscle hemoglobin per 100 gm. muscle.

As a general rule we feel that the content of muscle hemoglobin in striated muscle depends very largely upon work demand and exercise.

Short anemia periods (one to three weeks) will not show any corresponding change in the level of muscle hemoglobin in the striated muscle and this is a fortunate circumstance else an individual suffering from hemorrhage and severe anemia would die from muscular weakness. Long continued severe experimental anemia (hemoglobin 30 per cent of normal) lasting ten to twelve weeks may lower the muscle hemoglobin level of an active adult dog from 900 to 700 mg. muscle hemoglobin to somewhat lower levels—600 to 500 mg. muscle hemoglobin in skeletal muscle.[8]

TABLE I.—MUSCLE HEMOGLOBIN AND DIET.

Dog.	Age, wks.	Weight, kg.	Diet.		Blood hemoglobin, per cent.	Muscle hemoglobin, mg. per 100 gm.
			Bread.	Bread and liver.		
1	12	5.6	+	0	81*	234
5	13	7.5	−	+	87*	148
2	14	6.2	+	0	83*	211
7	14	7.5	−	+	90*	181
26–26	20	7.4	+	0	83†	354
26–27	20	6.8	−	+	112†	319
26–28	20	7.6	−	+	100†	379
26–25	20	6.6	+	0	119†	278
25–104	23	7.7	+	0	85	356
25–102	22	8.3	−	+	95	382
27–16	25	5.5	+	0	58	225
27–12	25	6.0	−	+	85	265
27–17	26	6.9	+	0	58	248
27–13	26	6.9	−	+	72	286
25–96	19	8.1	+	0	70	337
25–99	19	8.0	−	+	77	320
25–95	37	15.9	+	0	88	459
25–98	35	17.3	−	+	101	668

* Distemper.
† Distemper and blood concentration.

When we began the study of muscle hemoglobin it was a natural inference that muscle hemoglobin like blood hemoglobin might be influenced by diet factors. Blood hemoglobin is a labile substance subject to sudden fluctuations (accident and hemorrhage)*capable of rapid repair or renewal and perhaps rapidly used up and discarded in the body. By contrast we have shown[7] that muscle hemoglobin is not labile and is held tenaciously by the muscles in spite of severe anemia of $\frac{1}{3}$ to $\frac{1}{4}$ normal blood hemoglobin. Muscle hemoglobin is not subject to rapid fluctuations and we have no knowledge as to its wear and tear and replacement factors. When it is broken down in

the body bile pigment is one of the end products, as is true for blood hemoglobin.[10]

Blood hemoglobin production in the normal dog can be controlled at will by diet factors and this control can be readily demonstrated week by week. We hoped to demonstrate readily a similar influence of diet on the muscle hemoglobin content of striated muscles. We believe that Table I gives evidence that muscle hemoglobin is influenced by diet but the change is very slow and cannot be demonstrated in pups with less than fifteen weeks of diet control. After a period of twenty-five to thirty weeks there is a manifest difference in the pup fed standard bread and the litter mate fed standard bread plus equal parts cooked liver.

It may be possible to find a diet factor which will bring about a more prompt and striking change in the concentration of muscle hemoglobin within the voluntary muscles. We used our standard anemia bread[9] for the control group and a diet mixture of one-half bread and one-half cooked liver for the other group. We should test many other food factors but these experiments are quite difficult. Litters of pups after weaning must be fed carefully and individually, and the blood hemoglobin measured each week. In our large animal house, in spite of every precaution, these pups often become infected with distemper at ten to twenty weeks of age. This means complete loss of all animals and work done. The first two litters in Table I were infected with distemper and the experiments terminated—Dogs 1 to 7 and Dogs 25–26 to 26–28. Some of the fluctuations in blood hemoglobin and muscle hemoglobin in these animals are due to the distemper infection, loss of weight, loss of fluids, tissue dehydration and blood concentration. The last 3 litters in Table I show no distemper complications and one notes distinct changes in blood hemoglobin and muscle hemoglobin levels in the liver-fed pups as compared with the bread-fed controls. The difference is most notable in the last two oldest pups of thirty-five and thirty-seven weeks of age where the liver-fed pup shows a 30 per cent increase in muscle hemoglobin over the control. The litter mates of this pair killed and examined at the age of nineteen weeks showed no difference in the concentration of muscle hemoglobin in skeletal muscle.

Blood Hemoglobin. In contrast to the meager information relating to muscle hemoglobin we find a large amount of interesting data relating to blood hemoglobin. This is not the place to attempt a review of all this related work. Robbins and Whipple have published several papers[9,5,11] to show that blood hemoglobin regeneration in the dog can be completely controlled by diet. Evidence is slowly accumulating to indicate that similar diet control is possible in humans and this work has been stimulated by the important observations of Minot and Murphy[4] and others on diet therapy in pernicious anemia.

The anemia experiments from our laboratory have been described in considerable detail elsewhere and information as to the care of animals, methods, experimental procedure and so forth, may be found in these publications.[9] We may say in brief that the dogs are kept under *uniform conditions* of exercise, heat, ventilation, and so forth. The experimental anemia is maintained at a constant level of about 45 per cent hemoglobin or one-third normal by appropriate bleeding to give a continued maximal stimulus for hemoglobin regeneration. The hemoglobin removed is measured quantitatively in grams and this figure indicates the capacity of that dog to produce blood hemoglobin on the given diet intake.

The *standard bread* used in all these experiments consists of wheat flour, starch, bran, sugar, canned salmon, cod-liver oil, canned tomatoes, yeast and a salt mixture. This bread is mixed and baked by one of the technicians and supplies a complete diet capable of maintaining an adult dog in health for long periods if not indefinitely. On this standard bread diet a healthy anemic dog will regenerate 1 to 3 gm. hemoglobin per week period over and above his maintenance factor, which represents an unknown amount of blood hemoglobin worn out and wasted each week due to circulatory wear and tear. The standard bread was prepared to give the minimum amount of blood hemoglobin production in anemic dogs. In standard experiments we replace some or all of the bread by other food factors and the increased output of hemoglobin in the blood is obviously related to the added diet substance. Typical experiments with bread feeding are found in Tables IV and V.

TABLE II.—HEMOGLOBIN PRODUCTION INFLUENCED BY DIET.

Dog.	Table.	Diet, gm. per day.	Hemoglobin production per 2-week period, gm.
24–25	64	Bread, 450	3
19–104	71	Bread, 350	3
24–42	73	Milk, 450; bread, 450	3
19–104	71	Milk, 450; bread, 350	3
20–104	72	Cream, 100; bread, 350	12
24–45	72	Cream, 100; bread, 500	10
24–26	74	Butter, 100; bread, 350	10
24–46	75	Butter, 75; bread, 450	11
24–49	75	Cheese, 100; bread, 450	20
20–1	25	Beef muscle, 200; bread, 400	25
24–25	52	Pig muscle, 300; bread, 300	20
21–67	24	Heart muscle, 200; bread, 300	28
21–67	24	Codfish, 100; bread, 300	9
24–45	65	Fresh fish, 250; bread, 300	10
20–1	42	Spinach, 250; bread, 400	14
20–104	41	Greens, 200; bread, 300	20

To facilitate review of the results of our experiments Tables II and III have been prepared to show the relation between different diets and the production of blood hemoglobin in the anemic dog.

All other values which appear in standard experiments such as Tables IV and V have been omitted. The table column gives the table numbers under which may be found the various complete experiments published elsewhere.

Table II shows the low values for blood hemoglobin regeneration due to standard bread or to bread and milk feeding. Cream, butter and cheese are slightly more favorable for hemoglobin regeneration but we may say that as a rule bread stuffs and the common grains as well as dairy products are least potent of any diet factors as measured by their capacity to promote hemoglobin regeneration in the normal anemic dog. Dairy products contain many invaluable food factors but these foods are very poor in the elements which help the body to form new red cells and hemoglobin. This fact should be kept in mind by those who use dairy products liberally—for example in children's diets.

Skeletal *muscle* (beef, pig and sheep) varies widely in its capacity to produce new hemoglobin where fed in these experiments. The average values are probably fairly represented in Table II. Heart muscle as a rule is a little more potent than skeletal muscle. We may note that some smooth muscle—chicken gizzard Table III—is very rich in substances promoting blood hemoglobin regeneration.

Fish as a class stands with bread and milk. We incorporate some canned salmon in our standard bread. Fish liver and cod-liver oil were found to be inert. So too we see that whole fresh-water fish and dried cod fish have minimal influence upon hemoglobin regeneration in these dogs.

The *leafy vegetables* have a reputation probably much better than they deserve. Greens are supposed to be of rare potency to promote hemoglobin regeneration yet we can furnish no evidence of unusual blood regeneration following liberal diets of various greens. Beet greens, spinach, asparagus and lettuce all show values between 5 and 20 gm. hemoglobin production per two-week period above the control level. Other workers in experiments with herbivora have reported favorable influence of green vegetables in anemia periods. It is probable that herbivora can utilize chlorophyll or some of its split products to reconstruct new hemoglobin but there is no evidence that the dog can utilize chlorophyll in the diet to build new hemoglobin.

Liver stands at the top of the list of diet factors which are invariably most favorable for hemoglobin production in anemic dogs (Table III). From a great number of experiments it is obvious that the liver parenchyma contains a large amount of the material which can be built into new hemoglobin within the body. The storage of these hemoglobin parent substances in the liver cells we believe has some significance and we suggest that it is because the liver is so largely concerned with the complex internal pigment metabolism of the body. We believe the liver is concerned with

pigment conservation (Table V) and that the liver may be a most important organ in the fabrication of the amino-acid groups, which presumably are the parent substances of the hemoglobin which appears in its finished form within the red corpuscles of the red marrow. We find it impossible to think of the amorphous and inactive looking red cell as constructing within its protoplasm the complex protein hemoglobin and building it up from essential constituent building stones. We prefer to think of most of this early construction and grouping of amino-acids as taking place within the potent and active liver cell.

TABLE III.—HEMOGLOBIN PRODUCTION INFLUENCED BY DIET.

Dog.	Table.	Diet, gm. per day.	Hemoglobin production per 2-week period, gm.
19–104	23	Beef liver, 400	100
20–104	22	Beef liver, 300; bread, 300	50
24–49	62	Chicken liver, 200; bread, 250	75
24–25	64	Fish liver, 150; bread, 350	0
21–23	61	Beef kidney, 250; bread, 250	90
24–45	61	Pig kidney, 200; bread, 350	70
24–49	54	Chicken gizzard, 300; bread, 200	85
24–46	81	Bone marrow, powdered, 30; bread, 600	25
19–104	82	Beef spleen, 200; bread, 250	25
24–49	83	Brains, 300; bread, 300	25
24–25	84	Pig pancreas, 250; bread, 350	30
24–32	91	Apricots, 200; bread, 300	40
21–67	92	Peaches, 200; bread, 300	40
24–49	94	Raisins, 300; bread, 350	25
24–46	95	Apples, 250; bread, 350	35
24–49	97	Prunes, 250; bread, 350	35
24–49	97	Raspberries, 250; bread, 350	0

All mammalian liver so far tested contains large amounts of the unknown substances which favor production of blood hemoglobin in anemic dogs. There seems to be little or no difference whether the liver is fed raw or cooked in any simple fashion. Various extracts made by a variety of methods show potent substances in watery or alcoholic extracts as well as in the residue.[12] Chicken liver appears to be nearly if not quite as potent as beef, sheep, pig and calves liver but by contrast fish livers are uniformly inert.

Kidney stands next to liver and is quite potent in promoting hemoglobin regeneration in anemic dogs. We may search for the reason why renal epithelium should contain these parent substances for hemoglobin production. We know that hemoglobin set free in the blood stream will not escape through the kidney until a certain concentration of hemoglobin in the blood plasma is attained or we say there is a high threshold of renal excretion. This is a part of the remarkable reaction of the body to conserve hemoglobin in an emergency and rebuild it into new blood hemoglobin (Table V). It would seem that the kidney was concerned in this conservation of hemoglobin and that some of the building stones suitable for hemo-

globin construction were stored here. The anemia of nephritis may be related to the same phenomenon.

Bone marrow, spleen and *pancreas* are rated about the same and these tissues are only about one-third or one-fourth as potent as liver in promoting hemoglobin regeneration in anemic dogs. Brains come in the same group and this is surprising because of the low-protein content of brain tissue.

Fruits are of extraordinary interest because some of them are quite potent and others are inert—compare apricots giving 40 gm. hemoglobin production per two-week period, with raspberries giving no hemoglobin production over control levels (Table III). Because of the unexpected outcome of these experiments we have repeated them on several occasions with identical results. The explanation is not easy but these observations point strongly to *inorganic elements* as important in these reactions. A study of inorganic elements is now in progress.

TABLE IV.—FERRIC CITRATE PLUS PIG LIVER AND KIDNEY.

Dog 2446, Bull, Female, Adult. Splenectomy.

Diet periods 1 week each. Food, gm. per day.	Food conc., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hemat., per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed bled, gm.
Bread, 550; salmon, 100	63	18.7	1097	5.0	0.43	1.85	23.4	43	1.3
Bread, 450; salmon, 100*	95	18.9	1021	5.1	0.46	1.86	25.2	47	1.3
Ferric citrate, 0.25; bread, 400; salmon, 75	100	18.8	986	6.4	0.44	..	..	..	16.2
Ferric citrate, 0.25; bread, 400; salmon, 75	100	18.6	1063	5.5	0.59	1.92	29.0	56	32.4
Ferric citrate, 0.25; liver, 300†	100	18.7	947	5.4	0.66	2.14	27.9	60	28.5
Ferric citrate, 0.25; liver, 300†	100	19.3	962	5.0	0.82	2.19	22.6	49	76.5
Bread, 400; salmon, 75	100	18.9	1077	3.9	0.69	2.16	20.6	44	15.6
Bread, 350; salmon, 75	100	18.6	1003	3.6	0.67	2.17	22.1	48	1.4
Bread, 350; salmon, 75	100	18.6	1017	4.2	0.63	2.04	20.6	42	12.0
Bread, 350; salmon, 75	100	18.7	1036	4.1	0.54	2.00	22.3	45	1.3

Dog 2425, Bull, Female, Adult.

Bread, 550; salmon, 75	100	17.9	1133	4.2	0.43	1.98	18.4	36	1.2
Bread, 550; salmon, 75	100	19.0	1070	4.7	0.44	2.04	20.3	41	1.2
Bread, 550; salmon, 75	100	19.4	1155	4.7	0.46	1.99	21.5	43	1.4
Ferric citrate, 0.2; bread, 500; salmon, 50	100	19.6	1153	4.8	0.57	2.13	27.4	58	14.3
Ferric citrate, 0.2; bread, 500; salmon, 50	100	20.1	1130	5.6	0.47	1.84	23.0	42	20.1
Ferric citrate, 0.2; kidney, 300‡	100	20.3	1013	5.9	0.63	2.17	34.6	75	46.2
Ferric citrate, 0.2; kidney, 300‡	100	20.4	949	5.2	0.72	2.19	26.8	59	45.2
Bread, 500; salmon, 50	100	20.8	1107	4.2	0.70	2.08	28.6	60	39.4
Bread, 500; salmon, 50	100	20.7	1200	4.0	0.65	2.26	22.9	52	20.9
Bread, 500; salmon, 50	100	20.8	1137	4.2	0.65	2.00	18.6	37	18.0
Bread, 500; salmon, 50	100	20.7	1090	3.9	0.59	2.11	21.7	46	1.5

* Meat extract, 5 gm.
† Bread, 200 gm., daily diet.
‡ Bread, 300 gm., daily diet.

Iron is one of the inorganic elements which has received much attention by an army of investigators as iron is incorporated in the complex hemoglobin molecule. We may say as a rule in anemic dogs that iron by mouth in any form will produce a favorable reaction and much hemoglobin production if there exists an actual iron shortage in the body. Table IV illustrates a favorable reaction to ferric citrate, but we note that the subsequent diet periods of *iron plus liver* give the expected liver reaction superposed upon the iron reaction. There was a large excess of iron in the diet as the ferric citrate given amounted to ten times the content of iron in the liver ration. These experiments appear to separate sharply the iron effect from the liver effect. It has been claimed that the favorable effect of liver feeding was due to the combined iron in the liver parenchyma but these experiments should dispel this illusion.

TABLE V.—DOG HEMOGLOBIN GIVEN INTRAVENOUSLY.

Diet periods 1 week each. Food, gm. per day.	Food cons., per cent.	Weight, kg.	Plasma volume, cc.	R. B. C., millions.	Color index.	Hemoglobin index.	R. B. C. hemat., per cent.	Blood hemoglobin level, per cent.	Hemoglobin removed bled, gm.
Dog 2524, Coach, Male, Adult.									
Bread, 375; salmon, 100; klim, 25	100	12.4	788	5.0	0.42	1.80	23.4	42	1.2
Bread, 375; salmon, 75; klim, 15	100	12.2	788	5.1	0.41	1.83	23.0	42	1.2
Hemoglobin, total 6.2*	100	12.4	772	5.4	0.42	1.77	25.5	45	1.2
Hemoglobin, total 18.2*	100	11.9	710	6.4	0.45	1.75	25.8	45	29.0
Hemoglobin, total 22.4 *	100	12.6	750	4.9	0.46	1.75	25.8	45	1.4
Bread, 375; salmon, 75; klim, 25	100	12.7	744	5.8	0.45	1.88	19.9	37	24.4
Bread, 375; salmon, 75; klim, 25	100	12.7	744	3.8	0.49	1.88	19.9	37	1.1
Dog 2546, Bull, Female, Adult.									
Bread, 300; salmon, 75	100	10.5	589	3.9	0.40	1.81	17.3	31	1.0
Bread, 300; salmon, 75	100	10.7	668	4.4	0.43	1.75	22.0	38	1.1
Hemoglobin, total 3.7†	93	10.8	618	5.3	0.32	1.76	21.9	38	1.4
Hemoglobin, total 11.4†	97	10.7	560	6.6	0.44	1.80	24.1	43	15.7
Hemoglobin, total 15.5†	100	11.2	590	5.4	0.40	1.74	25.2	44	1.3
Bread, 350; salmon, 75; klim, 25	100	11.3	608	6.5	0.45	1.79	22.3	40	13.3
Bread, 350; salmon, 75; klim, 25	100	11.3	600	4.8	0.47	1.84	24.4	45	1.3

* Bread, 375; salmon, 75; klim, 15.
† Bread, 350; salmon, 50.

$$\text{Hemoglobin index} = \frac{\text{Hemoglobin, per cent.}}{\text{Red cell hematocrit, per cent.}}$$

Conservation of materials suitable for building of new hemoglobin in the body may be illustrated by Table V. The anemic dog conserves carefully even large amounts of injected blood hemoglobin and fabricates this material into new blood hemoglobin up to 90

per cent of all hemoglobin injected. It appears probable that this material is broken down at least in part to the essential building stones before being used for new blood hemoglobin production. A pancreatic digest of hemoglobin when given intravenously will appear after the usual interval (four to seven days) as newly formed blood hemoglobin. Here there may be only a 40 per cent conservation of these digestion products. It is highly probable that in emergencies the anemic dog can conserve *muscle hemoglobin* given intravenously to form new *blood* hemoglobin.

Fasting with its loss of body protein illustrates again the conservation of body material capable of being built into new hemoglobin in anemia. These dogs will show an increased output of blood hemoglobin during fasting periods as compared with control periods. Conversely during periods of rapid growth or rapid increase in body weight the anemic dog will show a notable *decrease* of hemoglobin production on a standard diet intake as compared with control periods. It appears likely that owing to this gain in weight some materials were used to form new body protein which otherwise would have been used to form new blood hemoglobin. This would indicate a certain amount of give and take between the tissue protein and blood-hemoglobin precursors.

Figure A represents a schematic picture of our understanding of general body pigment metabolism. Admittedly this is lamentably incomplete but may help the reader to visualize some of our knowledge and belief as to the construction, destruction, exchange and conservation of pigment elements within the body of the dog. "Urochrome" probably is derived from both "body protein" and "food protein" but has no direct relationship to blood or bile pigments according to the latest work. One is confident that blood and muscle hemoglobin are dependent upon food factors from which they are produced. We indicate by "pigment complex" the transition stage from food-split products to the finished hemoglobin. We may imagine this consists of a progressive synthetic grouping of amino-acids, iron and other materials which finally results in the finished product, hemoglobin. That this all takes place in the inactive red cell we cannot believe and prefer to think of much of this synthetic work being done by the liver cell, which is so active in all pigment metabolism.

Fasting experiments in which an excess of blood hemoglobin is produced indicate that from "body protein" katabolism the dog can conserve materials which are synthesized into hemoglobin—a beautiful illustration of the care taken by the body to conserve the elements suitable for new hemoglobin formation.

When hemoglobin is introduced intravenously, its pigment radicle may be all excreted as bile pigment, but usually some is stored away in reserve and the rest discarded as bile pigment. Given a severe anemia, we observe almost complete conservation of the injected

hemoglobin, which appears later as finished hemoglobin in red cells (Table V). The double arrows between "blood hemoglobin" and "pigment complex" indicate our belief that most of the injected hemoglobin is broken down before being rebuilt into new hemoglobin. Blood hemoglobin and muscle hemoglobin both contribute to the production of bile pigments as indicated in Figure A. This fact is amply supported by numerous experiments but we believe that diet may influence bile pigment output *directly* as indicated by the arrow between "pigment complex" and "bile pigment." We accept the hypothesis that all bile pigment may not be built up to hemoglobin and then broken down to bile pigment but surplus pigment-building material may be formed into bile pigment direct and so dis-

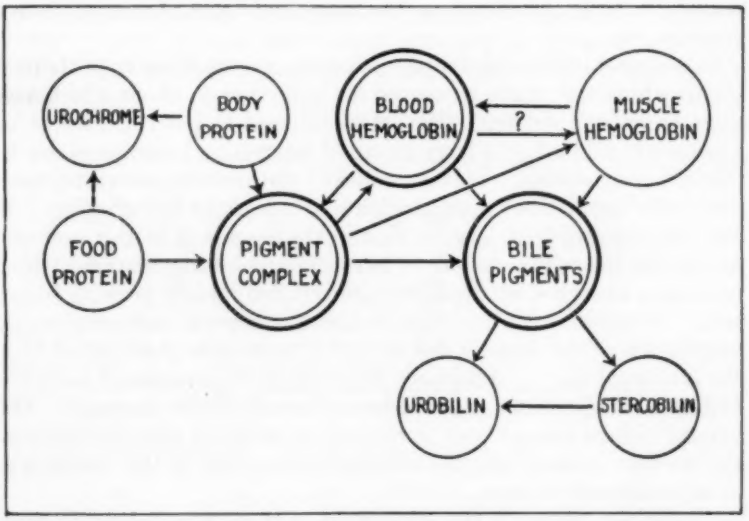

FIG. A.—Body pigment metabolism.

carded. We published experiments to support this hypothesis but these experiments were criticized by Rous and McMaster. We hope soon to publish more convincing experimental data, which we believe will establish our contention.

Is there a direct exchange between "muscle hemoglobin" and "blood hemoglobin" or the reverse? We believe the evidence is against this possibility and if certain exchanges do take place in anemia, myositis or other conditions it is likely that the hemoglobin concerned is broken down to intermediates ("pigment complex") before the reconstruction is effected.

We use the term "stercobilin" to indicate urobilin formed in the intestine. The absorption of stercobilin or urobolin from the intestine and its appearance in urine or bile is well established.[13] There

is doubt in our mind as to whether bile pigment as such is ever absorbed from the intestine. Our experiments have been completely negative and we do not accept the "circulation of bile pigments" as established. In any case there is no evidence that bile pigments ever contribute to the formation of any new hemoglobin in standard anemia experiments.

Anemia Problems. We are convinced that a wrong assumption has seriously hampered the study of certain human anemias. Attention has been focused upon hypothetical toxins which were supposed to destroy red cells *in vivo* and thus bring about the anemia. Because it can be demonstrated that a few types of anemia were due to toxic or parasitic destruction of red cells (septicemia, drugs, malaria), it was assumed that all other forms of anemia must be due to some hemolytic toxin produced in the intestinal tract, kidneys, tumor growths, etc.

It is almost impossible for physicians to give up these hypothetical toxins which they have treasured for many years, about which volumes have been written. Yet let us attempt to put them aside for a moment and look at a large group of interesting anemias as due to the *lack of something*. We may consider the anemias associated with tumors or nephritis or malnutrition and intestinal disturbances. It may be permissible to assume that in the anemia of cancer cachexia we are dealing with a default of hemoglobin building material which perhaps is absorbed by the more vigorous and rapidly growing tumor cells. Or again, with intestinal stricture or general malnutrition, we may find a severe anemia due to *lack* of materials unabsorbed from the intestinal tract. Again, we may look at the anemia of nephritis as due to faulty conservation of hemoglobin building material. The normal kidney plays a part in the conservation of pigment material and we may assume that the diseased kidneys fail in this function as in other excretory ones.

Pernicious anemia is the stronghold of those who believe in toxic red-cell destruction as the essential etiologic factor. A few years ago[6] we ventured the heretical belief that in this much-studied disease there was a *lack* of stroma building material but a great excess of all sorts of pigment and pigment-building material. The important observations of Minot and his collaborators may be interpreted as evidence in favor of a *lack* of a stroma-producing substance so that the pernicious anemia may prove to be a *deficiency disease*. It is difficult to reconcile the prompt remission in pernicious anemia due to liver feeding with a causative agent in the form of an intestinal toxin.

The anemia associated with bothriocephalus infections, which is often called pernicious anemia, has long been cited as the real proof of the toxic etiology of pernicious anemia. Yet when we examine the actual fabric of proof it is indeed a tenuous structure. This evidence has been recently reviewed carefully by Meulengracht[3]

and the interested reader is referred to his paper. He reviews all the known facts and admits that no direct evidence can be furnished for any demonstrable toxic substances in the bothriocephalus anemias, yet he concludes that pernicious anemia is due to an *obscure intestinal intoxication*. One can take each of his admirable deductions and use it with force to support the theory that pernicious anemia is due to *lack* of something.

We believe it will be profitable to reëxamine all of these anemias and search for a possible deficiency factor rather than for the elusive toxin. We believe it is not open to debate but may be accepted as established that simple anemias due to loss of blood can best be treated by means of diet therapy. Pernicious anemia has been shown to be amenable to diet therapy. Why not examine many other obscure anemias and marrow diseases for a possible deficiency factor? At least some interesting data will accumulate and may lead to a better understanding of a puzzling but important disease complex.

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OPHTHALMOPLEGIA IN GRAVES' DISEASE.

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The occurrence of ophthalmoplegia as a prominent symptom of Graves' disease is seldom seen. Because of the clinical picture of external ophthalmoplegia and a thyroid crisis, and the histologic findings in the thyroid, suprarenal and thymus glands, the following case study is of unusual interest.

Case Report. The patient, a woman, aged thirty-seven years, who was referred by Dr. Edytha Taylor, was admitted to Mercy Hospital on September 17, 1926. In 1914, the right lobe of the thyroid had been removed. The symptoms at that time had been nervousness, palpitation and rapid heart action and exophthalmus. There was no disturbance of vision and no limitation of ocular movements. Dr. Robert T. Miller, who cared for the patient at that time, has informed us that she suffered from typical exophthalmic goiter. She had a good recovery and was perfectly well until the onset of the present trouble. According to the patient, this began suddenly on May 30, 1926, when she had guests at her home. The family had noticed, however, that since the death of a brother three months before, over which she brooded, that she had been nervous, irritable and easily fatigued. The first symptom was diplopia which persisted for three weeks and then recurred at intervals for short periods. The patient noticed that her eyeballs were unusually prominent and that she was unable to move the eyes. At times slight movement of the eyeballs was possible during the early morning hours; weakness increased as the day advanced. This observation was confirmed during the first weeks in the hospital. There were also visual disturbances; at first she was able to read only the largest print. Then she experienced nervousness, weakness and palpitation. Her appetite had continued good, but she had lost weight. There had been no diarrhea. Perspiration had not been excessive, and the palms had remained dry. During the week before admission to the hospital swelling of the feet occurred. The thyroid gland was said to have fluctuated in size during the past twelve years. She stated that when tired or excited the gland was larger. At the first examination, the patient thought the gland was smaller than it had been. On June 22 she went to her physician because of double vision. After three weeks' rest in bed during which she took a small quantity of Lugol's solution she felt somewhat better. By the time she came to the hospital diplopia had ceased except for an occasional short period, usually early in the day. Ophthalmoplegia persisted, and she could read only very large print. The woman was nervous and subject to crying spells. She worried about herself and her child. Palpitation and undue fatigue occurred after slight exertion, so she was unable to do any housework.

The patient had had typhoid fever, scarlet fever and measles during childhood. Graves' disease first appeared when she was twenty-five years of age. She had married at thirty and had one child.

There was little that was relevant in the family history. The father died of apoplexy at fifty-two years of age. The patient was one of 14 children, 4 of whom died in infancy. One brother died of pneumonia. No other members of the family had suffered from goiter or any other recognized endocrine disorder. The family was of German extraction and was regarded as being emotionally stable, although the patient said that the mother and a few of the children "had a tendency to nervousness."

Physical examination. The patient was well developed, but she weighed only 97 pounds, and apparently had lost much flesh. There was slight cyanosis of the lips and finger nails. The vascularity of the skin was much increased. There was no edema. The soles of the feet were wet, but the palms were dry. *Eyes.* The eyeballs were prominent. There was partial ptosis which was bilateral and equal; each cornea was covered by the eyelid. The only movement of the eyeballs which could be effected was a slight turning of both eyes to the left temporal region. The eyelids could not be raised. The pupils were moderately dilated. The reaction to light was poor and contraction was not well sustained. The reaction to accommodation was likewise poor. The eyegrounds were normal. *Mouth.* There was severe pyorrhea and several decayed teeth were present. The tongue was

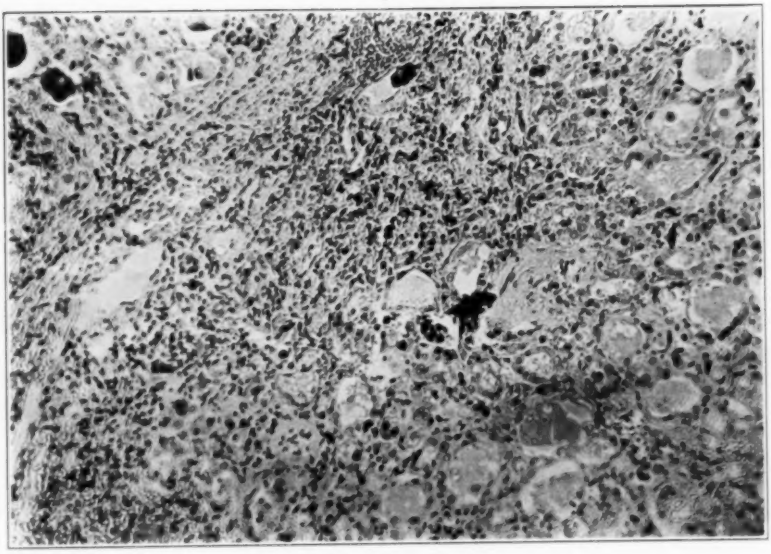

FIG. 1.—Section of thyroid.

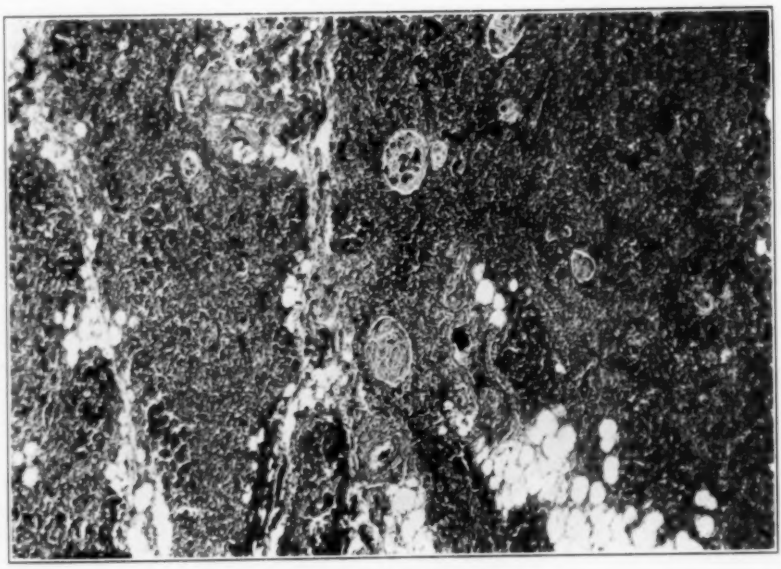

FIG. 2.—Section of thymus

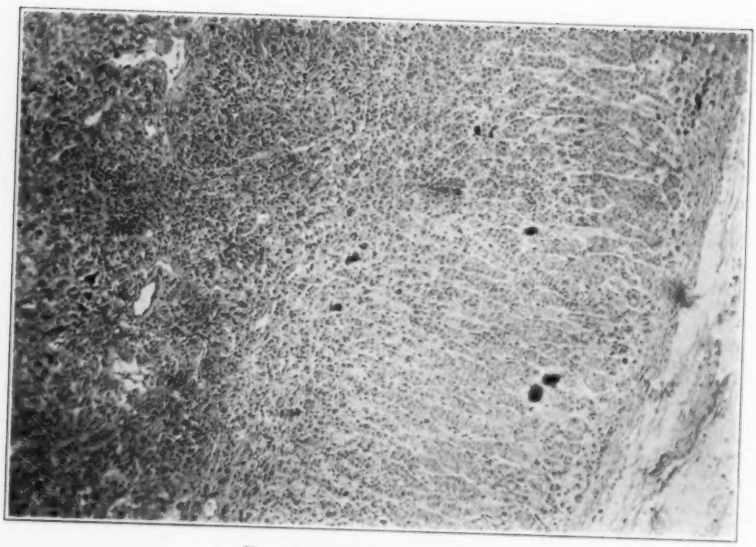

FIG. 3.—Section of adrenal.

clean. The tonsils were large but did not appear diseased. *Neck.* The jugular veins were slightly distended. At the base of the neck on the right side was a scar extending to the midline, the site of the former operation. The isthmus of the thyroid and entire left lobe were enlarged; the latter appeared to have the mass of a small orange with a long axis of about 8 cm. The gland was extremely hard, firm and smooth. The trachea did not appear to be displaced. (There had been no pressure symptoms.) *Glands.* There was no significant involvement of the lymph nodes. *Heart.* The heart was moderately enlarged and its activity was tumultuous. All sounds were accentuated. There was a harsh systolic murmur over the pulmonic area which was transmitted to the vessels of the neck and was heard over the thyroid. This murmur was faintly heard at the apex. The rhythm was normal with a rate of 156. The blood pressure was 152 mm. systolic, and 70 mm. diastolic. The peripheral vessels were normal. There was forceful pulsation of the abdominal aorta. The fluoroscopic examination showed a moderately enlarged, globular heart; the basal shadow was wide; there was vigorous aortic pulsation. An electrocardiogram taken on September 18 showed a normal rhythm interrupted by an occasional premature beat of the right ventricular type. The rate was 137 and the *P–R* interval 0.16 second. The *T* waves were inverted in Leads II and III. *Lungs.* The supraclavicular fossæ were sunken. The density of the apex of the right lung was increased. No râles were heard. By the fluoroscopic examination the lungs appeared normal. The diaphragm moved freely. The vital capacity was 1300 cc. *Abdomen.* There were no significant findings in the abdomen. *Neuromuscular.* The deep reflexes were active and equal, not appreciably exaggerated. The plantar response was normal. There was a fine tremor of the hands. The hand grip was fair. The patient was able to wrinkle the forehead only slightly. There was no paresis of the facial muscles. The involvement of the third, fourth and sixth nerves has been indicated in the description of the eyes.

The blood examination was normal except for a slight secondary anemia; the hemoglobin was 75 per cent; erythrocytes, 4,710,000; leukocytes, 7750, of which 72 per cent were neutrophils and 25 per cent lymphocytes. The Wassermann reaction was negative.

The renal function was practically normal. The urine gravity varied from 1003 to 1013. A trace of albumin was usually present. The microscopic examination of catheterized specimens was negative. The phthalein excretion for two hours was 44 per cent.

On September 18 the basal metabolic rate showed an increase of 44 per cent. On October 14 an increase of 22 per cent was reported but this reading did not correspond to the clinical picture at that time and doubtless did not represent the true metabolic rate.

Course. The patient was kept in bed and given luminal and 2 cc. of Lugol's solution daily. Improvement occurred promptly. She slept well, and the motor excitement decreased. By September 24 the blood pressure had fallen to 130 mm. systolic, and 65 mm. diastolic and the heart rate ranged from 80 to 90. She occasionally experienced double vision for a short time in the morning. The eyeballs sometimes showed greater movement. The patient herself was convinced that she should have another thyroid operation and would again be perfectly well. On September 25 she was examined by Dr. George J. Wright, who gave as his impression that the patient was suffering from myasthenia gravis due to disturbed endocrine balance, probably with thymus involvement. He suggested the use of calcium lactate and strongly advised against thyroidectomy.

That day the patient overheard a physician remark that he had seen a woman with similar findings who died. Thereupon the patient became

restless, she did not sleep that night and promptly returned to a state characterized by mental and motor excitement in which she appeared more toxic than when first seen. The circulatory activity increased and on September 29 the heart rate was 124 and the blood pressure 160 mm. systolic, and 78 mm. diastolic. The skin was dry and flushed, food was taken irregularly and she vomited frequently. She was irrational much of the time and always delirious at night. She had delusions of persecution and fear of death. Efforts were made to overcome the effects of the unfortunate remark, but they were only partially successful. During the first week in October there were short periods when she was rational, but she became rapidly worse. On October 8 the thyroid gland was much larger. By the middle of the month she was seldom quiet or rational and rest could be obtained only by the use of morphin and scopolamin. Larger doses of Lugol's solution were taken irregularly by mouth; it could not be administered by rectum. There were days when she was unable to swallow solid food and sometimes liquids were regurgitated. The rectal and vesical sphincters were frequently incontinent. Bilateral conjunctivitis developed but responded to treatment. Temporary improvement occasionally followed the intravenous or subcutaneous injection of glucose solution with insulin. Throughout this stormy period the patient exhibited great bodily strength. When she succeeded in escaping from her bed, it required three nurses to get her back. On October 17 the temperature, which had been low, rose to 102° by axilla and continued high with wide daily fluctuations until October 26; on October 22 it reached 105.6°. This fever was not accompanied by leukocytosis. The urine was normal save for a trace of albumin. There were no signs of meningeal irritation and a spinal-fluid examination gave normal findings. For five days during this period, cataleptic rigidity was present. On October 23 she first showed the reddish areolæ around the elbows and knees, said to be characteristic of a thyroid crisis. From October 26 to November 4 the temperature did not exceed 100° and there was slight improvement, but food was refused and nasal feeding was necessary. The blood pressure and the heart rate continued high throughout this period. Then the areaolæ decreased and disappeared from the right elbow. On November 6, she suddenly became quite rational, and took liquids freely, and recovery again seemed possible. However, the following day she became stuporous. The temperature rose; the heart rate was 230 and the systolic blood pressure 176 mm. and diastolic 90 mm. Redness of the elbows was again prominent. Digitolin was given intravenously and after twelve hours the heart rate was 180 with an irregular rhythm, probably that of auricular fibrillation. The lungs, which up to this time had remained clear, showed bronchial breathing over the apices and many râles throughout both lungs. When seen at 10 P.M. on November 8 she was resting quietly; the cardiac rhythm was regular, the rate 160. The following morning the nurses thought her appearance as usual. Death occurred suddenly at 7.20 A.M.

Pathologic Examination. Necropsy was performed at once. The body was much emaciated. The brain weighed 1220 gm. It was rather moist and there was considerable fluid in the subarachnoid space. The meninges showed no gross change. The pial vessels were congested. There was no evidence of gross pathologic change at the base of the brain, nor were there any areas of hemorrhage or necrosis. Serial sections revealed nothing significant. Microscopic examination of different parts of the brain, including the basal ganglia and medulla, showed no lesions. In this study, twenty-five areas were sectioned on each side, so that any type of encephalitis is definitely excluded.

The lungs showed acute bronchopneumonia; acute mucopurulent bronchitis; edema and congestion, and high-grade anthracosis.

The liver, kidneys, pancreas, spleen and ovaries showed no significant abnormalities.

The heart weighed 275 gm. The valves were normal, likewise the mural endocardium. The wall of the left ventricle was 1.25 cm. in thickness; the muscle tonus was good and on longitudinal section the muscle appeared healthy. Microscopically, however, there was seen a distinct decrease in the size of the heart muscle fibers and the staining reaction was rather faint. There was a diffuse increase in fibrous tissue without scar formation and in this new fibrous tissue were scattered lymphocytes and plasma cells. The bloodvessels were not sclerosed.

The elasticity of the aorta was good. The intima showed fatty streaking and near the bifurcation were numerous atheromatous plaques, some of which were calcified.

The organs showing significant changes were the thyroid, thymus and suprarenal glands. For much of the histologic description of these we are indebted to Dr. David Marine.

On opening the thorax, the lower portion of the thyroid gland was seen to extend to the suprarenal notch. The gland consisted of the isthmus and the left lobe; the latter was enlarged and of an unusually firm consistency. The gland weighed 90 gm. and measured 9 by 5 by 4 cm. The surface was lobulated and of a reddish-brown color. There were many fibrous adhesions attached to it anteriorly, especially over the lower half. On section, the cut surface was smooth and showed small translucent areas which alternated with grayish-yellow areas. Some portions of the gland were of pale red color but the general tone was a peculiar dirty ochre yellow. Sections showed that the majority of the acini were small and closely packed. Colloid was reduced but present in most of the follicles. There were areas showing medium-sized acini in which the colloid stained bluish (hematoxylin and eosin stain). In some parts the interstitial fibrous tissue was increased. The acinar lining cells were of the cuboidal type. The morphology of certain acinar lining cells was unusual; such cells were larger than the average cell of this gland and had a distinctly red cytoplasm of hyaline character and darkly stained nuclei. The nuclei were sometimes compact and irregular in outline, as in pyknosis; but many appeared dark because of an excess of chromatin. In all such cells the nuclei seemed disproportionately large, as well as dark. The pyknotic types showed less increase in size than those with the round or oval outline and excessive chromatin content. The latter were sometimes nearly as large as the cell, making them a striking feature of the section. Not all acini contained such cells, though they could be found in every field, and occasionally good examples were seen in two or three adjoining acini. There were no infoldings of the lining epithelium. A moderate degree of lymphocytic infiltration was seen, especially near the capsule. Marine suggests that these changes may indicate that the thyroid cells have been functioning under great strain, and that the final picture represents an exhaustion state in which cells in all stages of secretory activity are seen.

The principal portion of the thymus gland measured 5 by 4 by 0.6 cm. On section it presented the usual yellowish-gray, lobulated, glandular structure. There were large numbers of Hassall's corpuscles in all stages of formation, from single cells to large compound and concentric cell masses. In many places the reticulum was increased, apparently as a regenerative process. It showed a prominent epitheloid structure in which relatively few lymphocytes and some eosinophils were present.

The adrenal glands were of normal size and appearance. The cut surface showed a golden-yellow cortex and a dark-brown medulla. The glomerular zone of the cortex was decreased in width. Some of its cells were swollen, others were small; they were irregular in outline, finely granular and showed

dense pyknotic nuclei, whereas the normal cells have large vesicular nuclei. There was some connective tissue increase in this zone.

According to Marine, the important morphologic features of the thyroid, thymus and suprarenal cortex indicate that these tissues were undergoing tremendous activity and constitute the classic end stage of exophthalmic goiter.

Comment. Because of the ophthalmoplegia, the question arose as to whether that condition was part of the Graves' syndrome or was due to an independent disease. Chronic progressive ophthalmoplegia is extremely rare and almost always occurs before ten years of age.[1] The occurrence of high fever, restlessness, general psychic disturbance, inability to swallow and loss of sphincter control, in addition to the ocular palsies suggested at one time, epidemic (now endemic) encephalitis as the only disease capable of such protean manifestations. However, that was ultimately satisfactorily excluded by the detailed histologic examination of the brain. Approximately half of the cases of frank myasthenia gravis have ophthalmoplegia as the presenting symptom, and the ocular form of myasthenic paralysis is particularly common.[2] However, myasthenia gravis is a clinical syndrome whose etiology and pathology are unknown, whereas myasthenia, in the opinion of Marine, is a classic symptom of Graves' disease and may reach the degree seen in myasthenia gravis. In his monograph on myasthenic paralysis, Oppenheim[3] has stated that the symptom complex of myasthenic paralysis can be united with that of Basedow's disease; also, the disturbance of thyroid function in Basedow's disease increased the disposition to myasthenic paralysis. Subsequent writings may be divided into two groups; one in which the authors speak of the combined occurrence of myasthenic gravis and Graves' disease, implying the simultaneous existence of two clinical entities, and a second group who regard myasthenia as part of the symptomatology of Graves' disease. In 1904, Myerstein[4] wrote of the combined occurrence of myasthenia and Graves' disease and cited a case. More recently, Vedsmand[5] described a case as myasthenia gravis with symptoms of Graves' disease. It is clear in both of these instances that the presence of goiter antedated the appearance of myasthenic symptoms by several years.

In 1916 Heuer[6] discussed the cerebral disturbances of Graves' disease, reviewed the literature up to that time and cited a case of exophthalmic goiter which showed bilateral ptosis, complete external ophthalmoplegia, paresis of the motor fifth and seventh nerves, and profound muscular weakness; his patient died of acute respiratory paralysis; necropsy was not performed. Since that paper there have been a few clinical reports of ophthalmoplegia in Graves' disease, and most of the writers have considered myasthenia as a manifestation of the thyroid disturbance. Taylor[7] says that weakness of ocular movements is frequently present in Graves' disease,

and he mentions a patient who came for advice because of diplopia, without any other complaint or symptoms. DenBoer[8] describes the case of a woman who was observed for many years. Ten years after the onset of Graves' disease she developed difficulty in opening the eyes and later ptosis. Three years after that the left lobe of the thyroid was removed, following which he says the ptosis of the left eye could be considered cured, and for a period of years she had good movements of the eyelids. After four years more, ophthalmoplegia and complete ptosis of the lids returned. Jaensch[9] reported the history of a woman who had symptoms of a mild form of Graves' disease with exophthalmus, diplopia, and limited ocular movements. Following Roentgen ray treatment of the thyroid there was general improvement, but the ocular paresis was not favorably influenced. Rennie[10] has reported a case of "exophthalmic goiter combined with myasthenia gravis." His patient had symptoms of both diseases; there was no ptosis, but paresis of the external ocular muscles which gave rise to occasional diplopia; recovery occurred after ten years, but there were permanent defects of certain ocular muscles.

In some cases of myasthenia gravis, an enlarged thymus has been found and cases with tumor of the thymus have been reported. But in many cases of myasthenia gravis there has been no thymic involvement. The thymus and thyroid gland show parallel function. In goiter of adults enlargement of the thymus is usual. In a large series of cases of primary Graves' disease, Klose and Hellwig[11] found an increase in the epithelial structures of the thymus in from 70 to 80 per cent. These authors also describe thymogenic Graves' disease in which thyroid gland is said to be normal. In 1920, Marie and others[12] reported a case of progressive bulbospinal myasthenia with paroxysms of dyspnea and inability to speak or swallow, which for a period of five months reacted favorably to extract of whole suprarenal gland. Then the extract become ineffective and six months after the onset of severe symptoms the woman died of bilateral pulmonary edema, secondary to heart and kidney disease. The administration of adrenalin had been without effect. The most striking lesions were found in the muscles and the adrenal glands. The latter were hypoplastic and showed extensive change at the level of the medulla and the reticular substance, infiltration with lymphoid elements and cytolysis. More recently, Marinesco[13] has reported cases of myasthenia in which improvement followed the administration of adrenalin. He thinks that the muscle changes in myasthenia gravis are secondary to decreased oxidation and that the adrenal gland is primarily at fault. It is interesting to recall in this connection the work of Stewart and Rogoff[14] showing increased output of adrenalin following the giving of strychnin to dogs, inasmuch as strychnin has been the one drug on which dependence has been placed in the treatment of myasthenia gravis. But characteristic lesions of the adrenal glands are not constantly asso-

ciated with myasthenia. The interrelation of the suprarenal cortex, thymus and thyroid glands has been considered by Marine.[15] The present case is interesting in the light of these studies because of the morbid changes seen in the suprarenal cortex.

It seems justifiable to conclude, that for the case reported, the ophthalmoplegia can be accounted for adequately by the disturbance in the thyroid or adrenal glands and that it was not present as a symptom complex independent of the Graves' disease.

Summary. A case of recurrent Graves' disease is reported in which the symptoms began with visual disturbances due to external ophthalmoplegia, and death resulted during a thyroid crisis. The postmortem examination revealed changes in the thyroid gland believed to represent an exhausted state. There were degenerative changes in the adrenal cortex, while the thymus showed an unusual degree of degeneration. The occurrence of ophthalmoplegia in Graves' disease has been considered and the relation of myasthenia to changes in the thymus and adrenal glands. The ophthalmoplegia in the case studied is believed to have been a part of the Graves' syndrome and not an expression of an independent symptom complex.

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HYPERTHYROIDISM AND DIABETES.*

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If desiccated thyroid or any other thyroid preparation is fed to a patient, the blood sugar rises and glycosuria appears, as can be seen in Fig. 1. Cammidge and Howard[1] have shown that the rise of

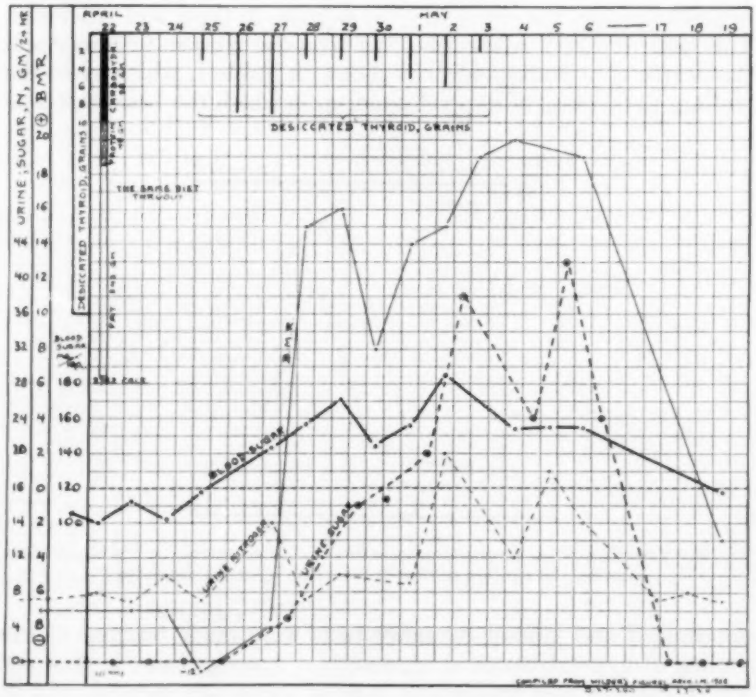


Fig. 1.—The effect of thyroid feeding on blood sugar, urine sugar, urine nitrogen and basal metabolic rate. (After Wilder.)

blood sugar which follows the ingestion of thyroid extract is proportional to the size of the dose (Fig. 2). That which has thus been demonstrated experimentally apparently happens also in many cases of hyperthyroidism in which there appears either slight, moderate or marked hyperglycemia with glycosuria or glycosuria alone without any rise of blood sugar above the physiologic limits. Geyelin[2] thus reports the occurrence of hyperglycemia in 90 per cent of a

* Read before Inter-state Postgraduate Assembly, Kansas City, Mo., October 17–21, 1927.

series of moderate and severe cases of hyperthyroidism (27 cases). I have thus far found nonphysiologic hyperglycemia 285 times in a series of 3335 cases of hyperthyroidism. In this series of cases I made 150 glucose-tolerance tests (giving 100 gm. of glucose by mouth on a fasting stomach). These curves varied from normal to that type of curve which characterizes the most severe type of diabetes (Fig. 3). It is of special interest to note that these curves do not run parallel with the severity of the hyperthyroidism so that in a mild case of hyperthyroidism the curve may be of the latter type, that is, that characteristic of severe diabetes; while in a severe case of hyperthyroidism the curve may be normal in type, and *vice versa*. This lack of direct relationship between the glucose tolerance and the degree of hyperthyroidism is shown in Table I, which gives the findings in 66 cases of hyperthyroidism in which the basal rate was

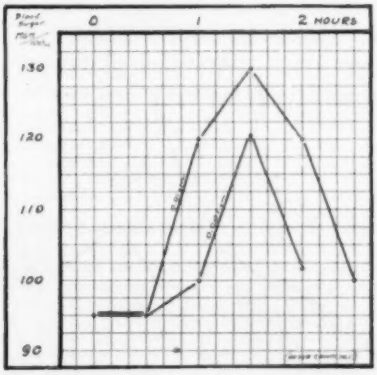


FIG. 2.—The effect of the intravenous injection of thyroid extract on the blood sugar, showing the relation of dose to the rise. (After Cammidge.)

determined and glucose-tolerance tests were made because of the finding of hyperglycemia or glycosuria. Among these, in 60.6 per cent a diabetic and prediabetic type of curve was secured, and in 39.4 per cent a normal curve. Since there seems to be no direct relationship between the severity of the hyperthyroidism and the carbohydrate tolerance, we cannot say that the carbohydrate disturbance when it is present is due solely to the toxicity of the thyroid secretion, but must look elsewhere for the cause.

Why is it that in many mild cases of hyperthyroidism there is a lack of carbohydrate utilization, as evidenced by excessive postprandial hyperglycemia, while on the other hand, in many very severe cases there is a normal utilization of carbohydrate? We cannot explain the abnormal curves on the basis of obesity, for though obese individuals often show a decreased glucose tolerance, most patients with hyperthyroidism are not obese but have lost

much weight; in my series 33.3 per cent were overweight and 66.6 per cent underweight.

In 1917, Naunyn[3] made the following statement: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria

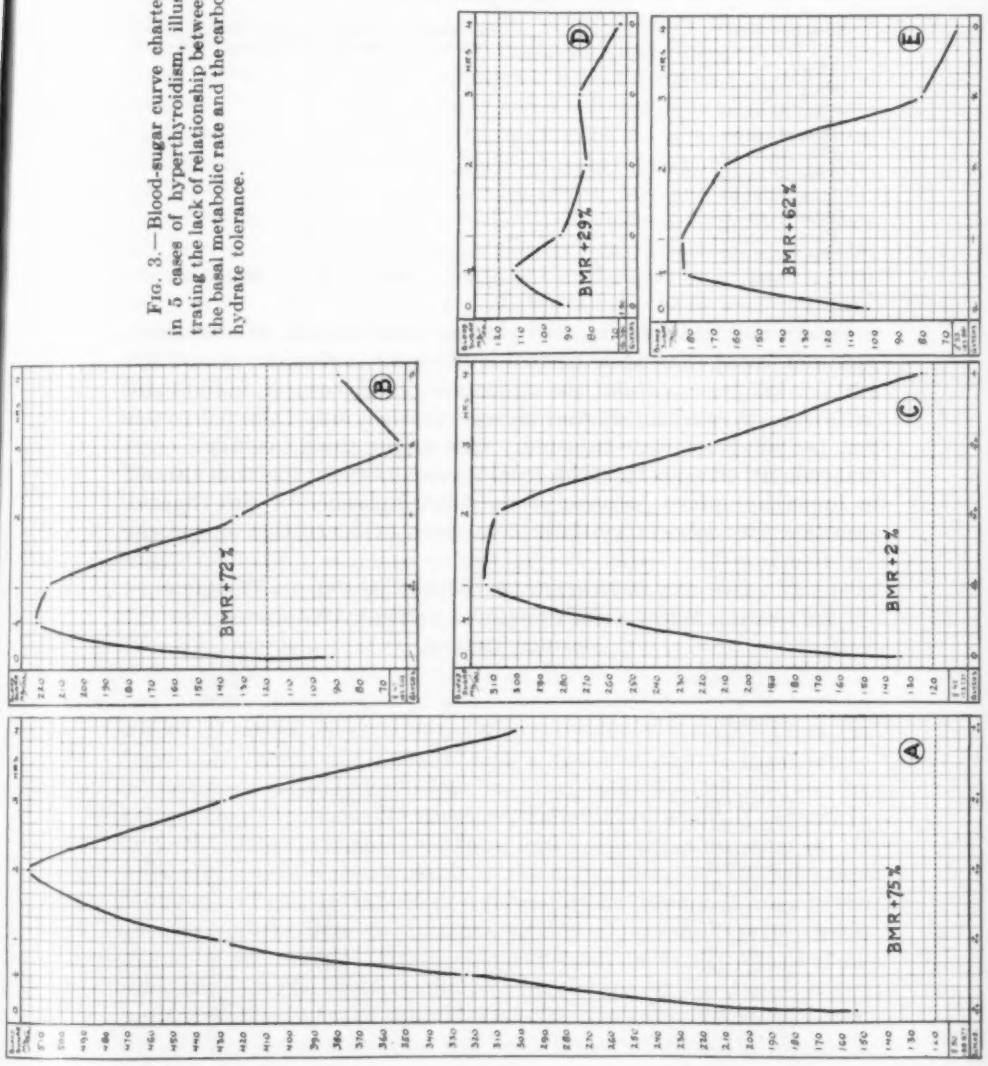


Fig. 3.—Blood-sugar curve charted in 5 cases of hyperthyroidism, illustrating the lack of relationship between the basal metabolic rate and the carbohydrate tolerance.

only when there exists a predisposition (Anlage) to diabetes." And the following statement by von Noorden[4] is also pertinent—"Pure hyperthyroidism in the presence of a fully normal chromaffin system

and a normal pancreas will very seldom produce an alimentary and spontaneous transitory glycosuria."

TABLE I.—THE RELATION OF THE BASAL METABOLIC RATE TO THE GLUCOSE TOLERANCE.

Basal metabolic rate.	Number of cases.	Diabetic or pre-diabetic curve.	Normal glucose tolerance curve.
Minus	3	2	1
Plus 1 to 10	11	5	6
Plus 10 to 20	8	3	5
Plus 20 to 30	11	7	4
Plus 30 to 40	10	5	5
Plus 40 to 50	10	8	2
Plus 50 to 60	4	3	1
Plus 60 to 70	4	4	0
Plus 70 to 80	4	2	2
Plus 80 to 90	1	1	0
Total	66	(60.6%) 40	(39.4%) 26

Wilder and Sansum[5] injected glucose intravenously at a uniform rate and found that while normal individuals could take care of 0.8 gm. per kilogram without the appearance of glycosuria, individuals with hyperthyroidism showed glycosuria when only from 0.5 to 0.6 gm. per kilogram were injected. One might think, as Allen once pointed out, that perhaps the renal permeability for sugar is altered in hyperthyroidism because of the toxic influence of the thyroid secretion; but laboratory data have given evidence that in certain

TABLE II.—THE RENAL THRESHOLD AS DETERMINED IN 73 GLUCOSE-TOLERANCE TESTS MADE IN CASES OF HYPERTHYROIDISM AND SIMPLE GOITER.

Level for renal threshold. Blood sugar, mg., per 100 cc.	Number of cases.
60 to 70	3
71 to 80	3
81 to 90	0
91 to 100	6
101 to 110	3
111 to 120	11
121 to 130	7
131 to 140	4
141 to 150	4
151 to 160	7
161 to 170	5
171 to 180	4
181 to 190	1
191 to 200	1
201 to 210	3
211 to 220	2
221 to 230	4
231 to 240	1
241 to 250	1
251 to 260	1
261 to 270	1
271 to 280	0
281 to 290	0
294	1

cases the opposite condition prevails. It is true that in hyperthyroidism the renal permeability is somewhat increased, as is shown in Table II, and this fact might in part explain the findings of Wilder and Sansum if it were not for further evidence collected from the study of blood-sugar curves which show a definite lack of carbohydrate utilization—if we accept the interpretation that abnormal hyperglycemia means a decreased utilization and storage of carbohydrate, and that this in turn indicates a lessened amount of available insulin. While in many of these cases of hyperthyroidism the fasting-blood sugar is normal, yet they present an abnormal response to glucose, as is evidenced by the high prolonged curve—an observation which has also been made by Denis, Aub and Minot.

As Cramer and Krause[6] have shown, in cases of hyperthyroidism the liver is practically free from glycogen so that this factor alone ought to prevent an abnormal rise of blood sugar, as in the absence of glycogen in the liver one would expect it to be stored promptly after the ingestion of the large amount of carbohydrate which is given in the tolerance test. Since the liver does not take care of it but sends it on through the blood stream, one can but think that there must also be some interference with the storage of glycogen. The storage of glycogen, as has been shown by Best, Hoet and Marks[7] and by Lawrence,[8] is accomplished through the influence of insulin, and, therefore, the lack of glycogen storage indicates a shortage of insulin. In hyperthyroidism, then, there are two factors which indicate a shortage of insulin: (*a*) Abnormal postprandial hyperglycemia; (*b*) a glycogen-free or glycogen-poor liver which is unable to store added glucose. Against this statement one might offer the argument that the hyperglycemia is due to some toxic effect of the thyroid secretion, but this assumption can be ruled out by the fact that hyperglycemia is sometimes present in mild cases and absent in severe cases, whereas if it were due to toxicity alone the degree of hyperglycemia should bear a direct relation to the severity of the case. The glycogen-free liver can easily be explained on the ground that the markedly increased metabolism which is present in hyperthyroidism exhausts its store and keeps on exhausting it. If sufficient insulin were available in the body, however, the ingestion of 100 gm. of glucose should be followed by its prompt storage in the muscles and the liver as glycogen, so that abnormal hyperglycemia should be prevented. This problem can only be finally solved when sufficient data can be accumulated whereby to compare the glycogen content of the livers of individuals with hyperthyroidism in whom the carbohydrate tolerance has been impaired with the livers of individuals with an intact insulogenic apparatus, as evidenced by an unimpaired carbohydrate tolerance.

Aside from its academic interest, however, the most important question presented by this whole problem is the following: What happens to those patients who show a decreased tolerance; does the

carbohydrate tolerance become normal, or does the condition progress until frank diabetes is developed?

As has been reported by numerous authors—Denis, Aub and Minot;[9] Holst;[10] Rohdenburg[11] and others, in many of the milder cases the carbohydrate tolerance becomes normal after thyroid-

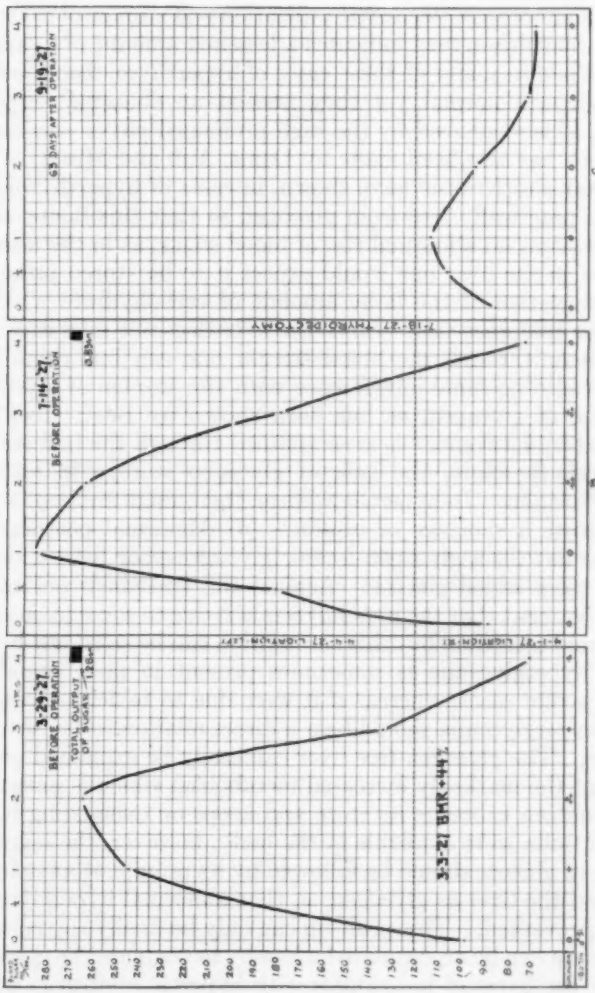


FIG. 4.—Three glucose-tolerance curves made in a case of hyperthyroidism, that of a man aged fifty-one years; *A* and *B*, before; *C*, sixty-three days after thyroidectomy.

ectomy. In Fig. 4 is shown a chart which gives striking evidence of such a restoration. The three glucose-tolerance curves illustrated here were made in a severe case of hyperthyroidism in a man, aged fifty-one years, with a basal metabolic rate of +44. Glucose-tolerance tests made before and three months after thyroid-

ectomy gave the type of curve which is characteristic of severe diabetes. The patient was kept on a diabetic diet and five months after the operation the glucose-tolerance curve was normal. In other cases in which I have had opportunity to recheck the glucose tolerance, an improvement is shown which seems to be proportional

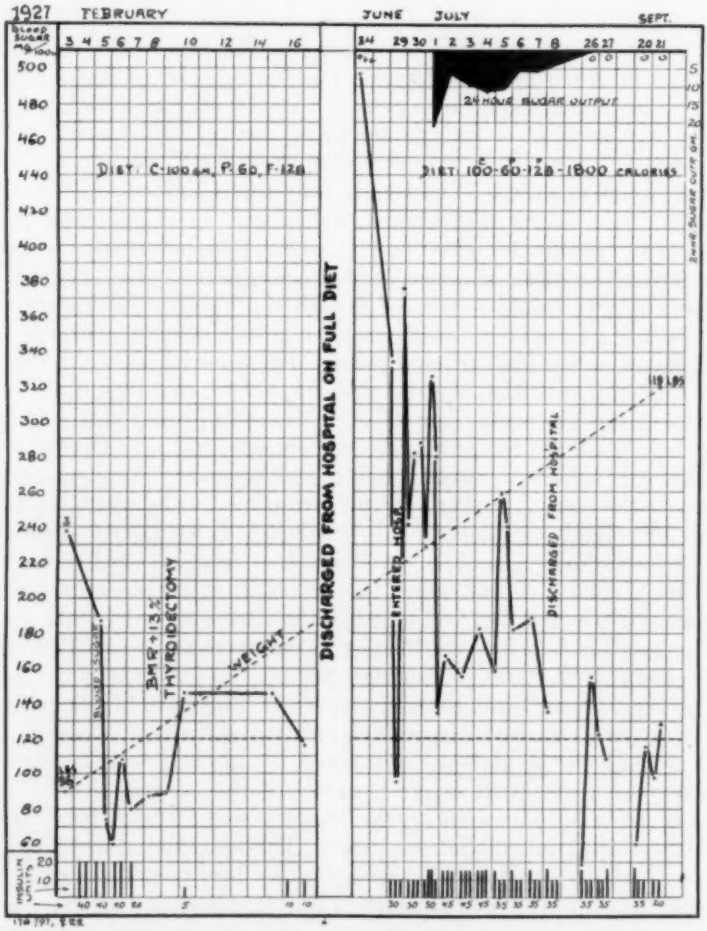


FIG. 5.—Blood-sugar observations in a mild case of hyperthyroidism, that of a girl aged twenty-two years, showing disappearance of the hyperglycemia under suitable diet and insulin and its reappearance when dietary control was discontinued.

to the care exercised in the diet. When the prescribed diet has been disregarded, either wilfully or as the result of misdirection, the evil result is promptly manifested by the glucose tolerance curve. This is well illustrated by the curves shown in Fig. 5, which were made from blood-sugar estimations in the case of a young girl, aged twenty-

two years, in whom when first seen the blood sugar three hours after a meal was 238 mg. per 100 cc. The blood sugar was quickly restored to the normal level as the result of a prescribed diet and insulin and it remained within normal limits even after the insulin was discontinued, showing only a slight rise after thyroidectomy, after which it quickly returned to normal. For four months after this patient was discharged from the hospital, however, the prescribed diet was disregarded, and when she was again seen four months later her blood sugar was 496 mg. per 100 cc. and she had heavy glycosuria and acetonemia; that is, she presented all the classical symptoms of diabetes for which she had to be treated in the routine manner. Two other similar cases have come under my observation so that I feel strongly that these high hyperglycemias are far from being meaningless, and that, therefore, these cases should be followed for a long enough period for us to feel certain that the patient's weakened tolerance has been restored. In other words, these patients should be treated as diabetics. They should be given a carefully selected diet of sufficiently high-caloric value with enough insulin to buffer the carbohydrates. These measures will improve the general condition of the patient before the operation, will increase the glycogen reserves in the liver, will decrease acidosis, will help maintain the proper glycogen reserve in the cardiac muscle of a heart which is already being overworked. These measures apparently have no other specific action on the hyperthyroidism; they are merely physiologic aids which help to support and restore the overworked organism. It is true that in many such cases the patient's condition will return to normal after thyroidectomy even without a selected diet, without insulin, and if we only could know beforehand in which cases this restoration would occur, a great deal of routine work could be eliminated.

In Figs. 6 and 7 are given charts which illustrate like degrees of improvement secured respectively with and without insulin. In Fig. 6 is given the glucose-tolerance curve in the case of a woman, aged sixty years, with severe hyperthyroidism and diabetes. Her blood sugar on admission to the hospital was 219 mg. per 100 cc. and her basal metabolic rate +41. This patient adhered to the prescribed diet and insulin dosage after her discharge with the result shown in the second curve in Fig. 6. Note the improvement demonstrated by the second curve and the lessened glycosuria. Eight months after her operation the patient was in perfect health. But although her fasting blood sugar was quite normal, that is, only 79 mg. per 100 cc., yet at the end of the second hour of the glucose-tolerance test, when it should be back to the normal level, there was a tremendous rise up to 338 mg. per 100 cc.; while at the end of the fourth hour it was still 168 mg. per 100 cc. The third tolerance test, which was made eight months after the second test, showed a further improvement, and the fourth tolerance test made six months

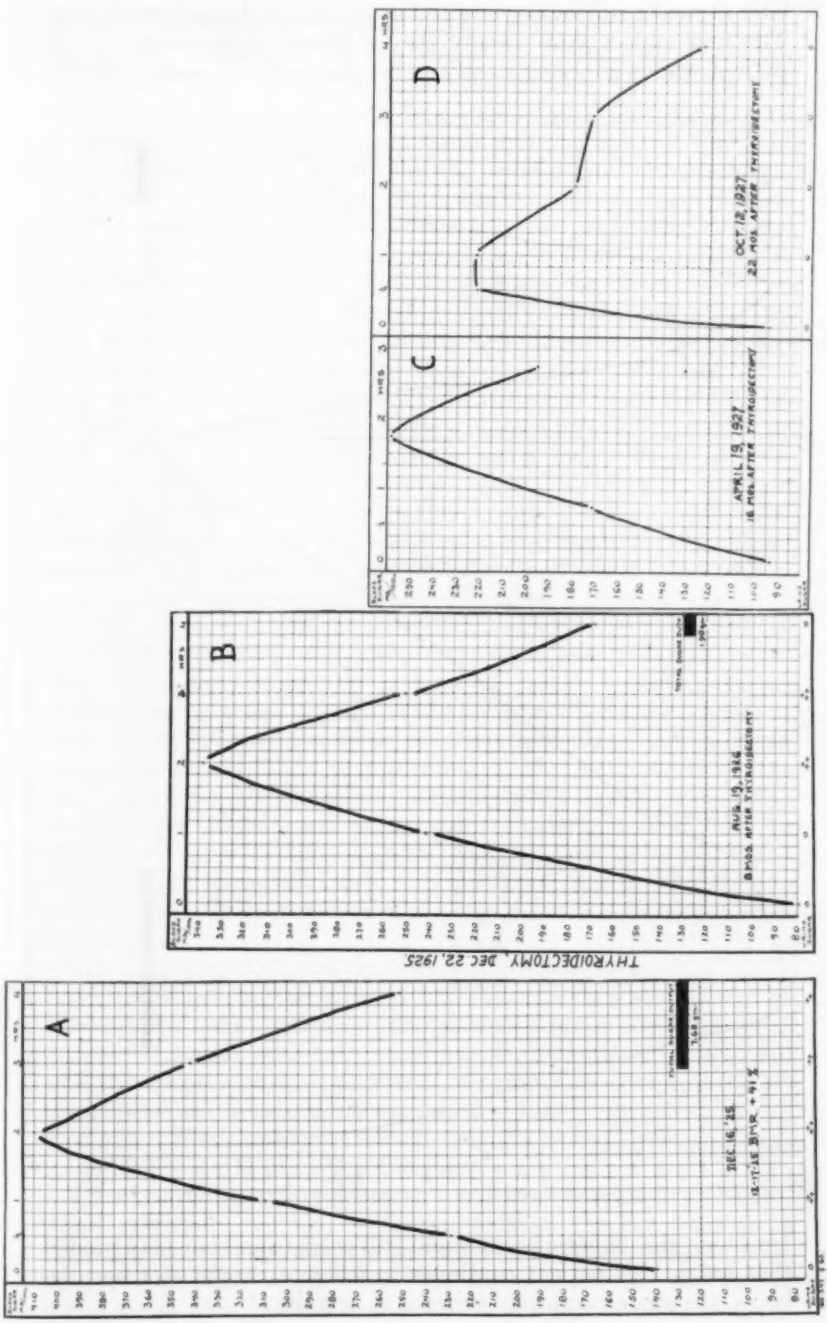


FIG. 6.—Glucose-tolerance curves in a case of hyperthyroidism; *A*, before; *B*, *C* and *D*, after thyroidectomy. This patient received insulin and was on a controlled diet.

later showed a still lower curve and no glycosuria throughout the test. The four curves show clearly the continued improvement of the patient who is adhering closely to her diet and is in perfect health.

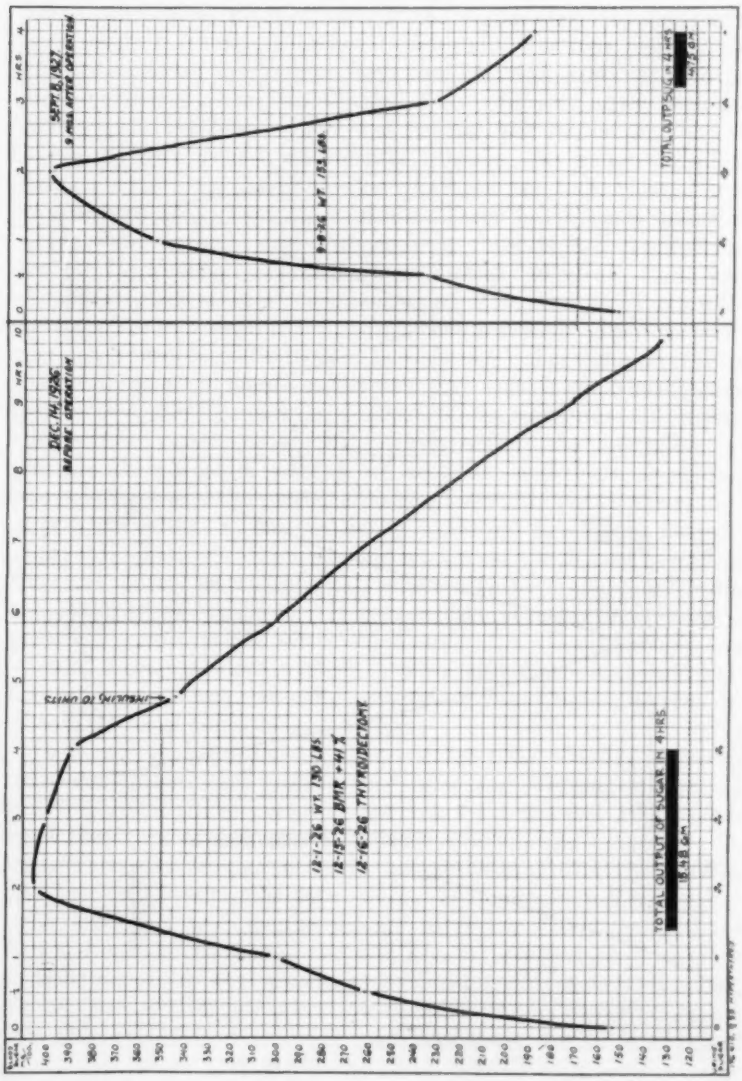


FIG. 7.—Glucose-tolerance curves in a case of hyperthyroidism; *A*, before; and *B*, after thyroidectomy. This patient was not on a controlled diet and received no insulin.

However, the diabetic background still persists and one may predict that unless this patient continues to follow a careful diet her diabetes will almost certainly increase in severity.

On the other hand, the curves shown in Fig. 7 demonstrate

similar improvement in a case in which neither diet nor insulin was employed. This case is that of a woman, aged fifty-nine years, with hyperthyroidism. Her blood sugar on admission was 169 mg. per 100 cc. three hours after a meal and examination of the urine showed glycosuria 4+. Of the two glucose-tolerance tests the curves of which are shown in Fig. 7 the first was made before thyroidectomy, the second nine months after the operation. Though the peak of the curve and the fasting blood-sugar level are practically identical in both curves, nevertheless the second curve shows a considerable improvement in its descent which is rapid and the chart shows also a decreased sugar output. The point of interest in this case is the fact that the patient had not been on any prescribed diet in the interim between these two tests, so that whatever improvement had taken place must be ascribed solely to the elimination of the thyroid gland.

These 2 cases then offer evidence in support of the statement made above, namely, that in some cases improvement follows thyroidectomy, provided a dietary regimen is followed; while in others improvement occurs without any dietary observance. Nevertheless, the curves of both of these cases make it evident that neither of these patients is a normal individual with an intact insulogenic function but that each has a mild degree of diabetes which will become severe on any slight provocation unless some change in the insulogenic apparatus takes place in the meantime. It seems to me that these charts show also that as far as the impaired glucose tolerance is concerned it is not the hyperthyroidism *per se* that is at fault, for if that were the case then, given sufficient time, complete restoration should follow thryoidectomy. But, as is shown by the charts, such is not the case and apparently the damage wrought in the islands of Langerhans is permanent. In 1909, Sattler[12] collected 56 reported cases of diabetes and hyperthyroidism, 37 of which had been followed for a sufficiently long period of time to offer definite information. Of these, 67 per cent died a short time after operation, 7 in coma.

The influence which the development of hyperthyroidism has on the blood sugar can be gleaned from the charts given in Fig. 8. These charts were made from four glucose tolerance tests made in the case of a man, aged thirty-four years. The curves of 1922 and 1924 are almost identical; while that of 1926, made after mild hyperthyroidism had developed, shows a considerably increased hyperglycemia. The final curve which shows a normal tolerance was made three months after thyroidectomy.

The effect of hyperthyroidism on the glucose tolerance can be produced artificially, namely, by thyroid feeding. In Fig. 9 are given three tolerance curves made in the case of a markedly obese woman, aged twenty-eight years. The first curve is normal; the second curve shows what thyroid feeding did to the glucose tolerance; the curve shows the return to a normal tolerance four months after thyroidectomy.

Cases in which diabetes resulted from thyroid feeding have been reported by numerous authors: Mueller,[13] 2 cases; Rohdenburg,[14]

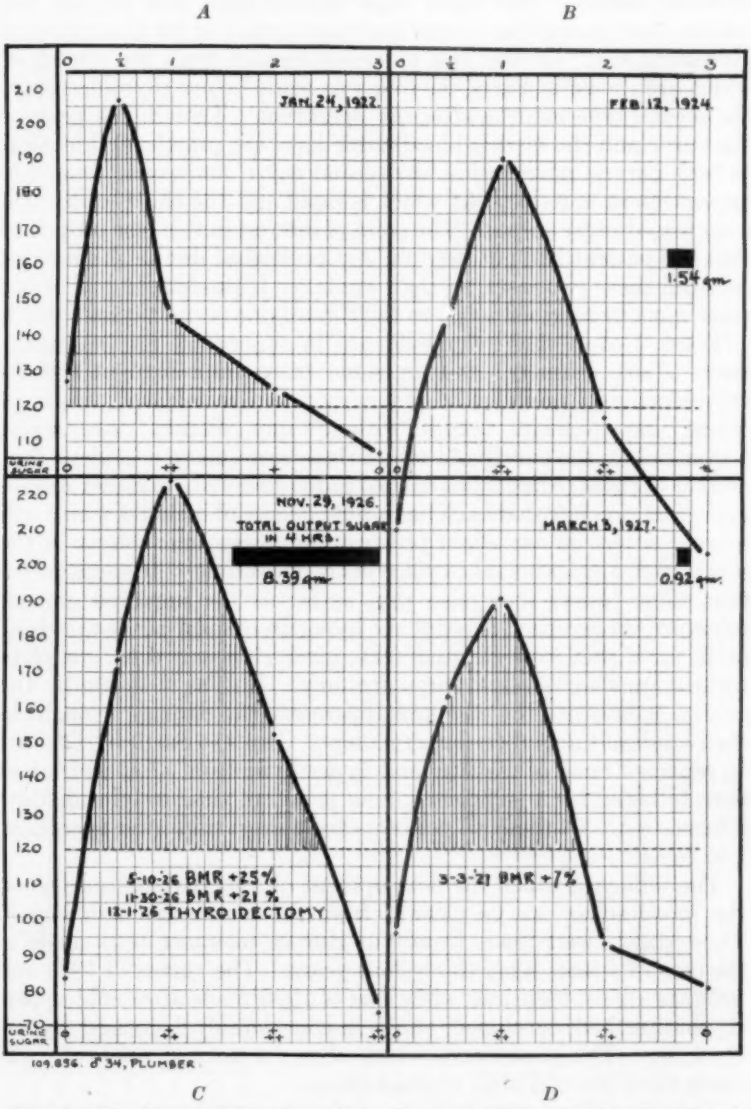
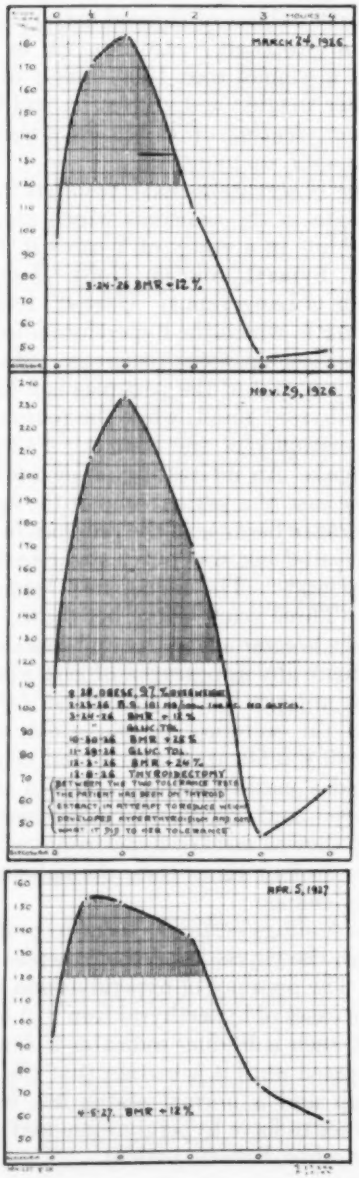


FIG. 8.—Blood-sugar curves in a case of hyperthyroidism showing the effect of the hyperthyroidism on the carbohydrate tolerance, *C*, and the improvement following thyroidectomy, *D*.

4 cases; Garrod,[15] 5 cases; Notthaft,[16] 1 case; Ewald, 1 case. That this does not always happen, however, is shown by other cases, such,



A

B

C

FIG. 9.—Blood-sugar curves in the case of an obese woman with hyperthyroidism, showing in *A* a normal carbohydrate tolerance before the thyroid feeding was started; in *B*, the effect of hyperthyroidism which was induced by thyroid feeding; and in *C*, the effect of thyroidectomy.

for instance, as that reported by Becker[17] in which a boy, aged two and a half years, ate 90 tablets of thyroid extract and did not even show glycosuria; and Notthaft's case No. 43, in which during a period of five weeks a woman took 1000 tablets of thyroid extract in order to reduce her weight; and glycosuria and hyperthyroidism developed, the former clearing up in ten days though the thyroid remained hyperactive for six months.

Certain interesting observations have resulted from the study of the pathologic changes in the pancreas which are associated with hyperthyroidism. Thus in a study of 4 cases in which glycosuria was associated with hyperthyroidism Holst[10] found a diminished number of the islands of Langerhans. Garrod[15] refers to a few cases of exophthalmic goiter in which the hyperthyroidism was associated with atrophy or other lesions of the pancreas. Marinesco and Parhon[18] state that the removal of the pancreas is followed by signs of overfunction of the thyroid gland; while the removal of the thyroid is followed by hypertrophy of the islands. Falta[19] and Lorand[20] report similar changes. An interesting observation is reported by Rhodenburg,[11] in the case of a patient who at the age of thirty years was refused life insurance because of the presence of glycosuria. She was subsequently treated but was never sugar-free. During seven years she lost 35 pounds. The menopause began when she was forty years of age. Three years before her death, with the passing of the menopause, she became sugar-free and was able to eat heavily, even of candy, without any appearance of glycosuria. She died in nephritic coma. At autopsy the thyroid gland showed almost complete destruction of the secreting alveoli, which were replaced by connective tissue richly infiltrated with round cells. The head of the pancreas showed a marked fibrosis, most of the glandular elements being destroyed, and only an occasional island of Langerhans persisting; the body showed marked hypertrophy of the islands, most of these being three to four times their normal size; the tail of the pancreas showed no change.

These pathologic findings certainly seem to point to some interrelationship between the thyroid and the pancreas.

Conclusions. 1. The presence of hyperglycemia with glycosuria is not a rare finding in cases of hyperthyroidism. A safe and workable assumption is that such a finding indicates a functional diabetes, which should be treated until it is certain that the functional weakness has cleared up and a normal status has been restored. A patient who continues to have hyperglycemia and glycosuria should be treated like any other diabetic patient.

2. The degree of hyperglycemia bears no relation to the severity of the hyperthyroidism or to the height of the basal metabolic rate. It would appear therefore that this condition of lowered carbohydrate tolerance is not due to the hyperthyroidism *per se*, but rather

that this is but the provocative factor, and that the direct cause is to be sought in the insulogenic apparatus.

3. Thyroidectomy improved the carbohydrate tolerance, mild disturbances of which disappear after operation, while in more severe cases the condition is ameliorated.

4. In cases of hyperthyroidism in which hyperglycemia is present the preoperative routine should include a sufficiently high caloric diet, together with the admistration of small doses of insulin, in order that the glycogen-poor or glycogen-free liver may be restocked. In mild cases of hyperglycemia this will prove a useful—in severe cases an essential—supporting measure.

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TRANSIENT INSULIN HYPOGLYCEMIC HEMIPLEGIAS.

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Since insulin has become indispensable in the treatment of diabetes mellitus, various untoward effects have been obtained from it in the hands of almost everybody engaged in diabetic work. Numerous observations have been made in the literature for the last five years regarding the various phases of the so-called "insulin reactions," or, as Fletcher and Campbell[1] first named it, "symptom-complex hypoglycemia." This, for sake of accuracy, should always be termed "*insulin* hypoglycemia symptom complex," as a non-insulin hypoglycemia *per se* will not necessarily produce the same clinical picture (*vide infra*). That insulin is in relation to this train of symptoms as cause to effect is well established by the almost dramatic antidotic-like effect of treatment by glucose or adrenalin, which has in its aim the repletion of the lowered sugar concentration in the blood caused by insulin overdosage.

Among the symptoms and signs observed by various authors in insulin hypoglycemic reactions, one may cite by way of *summary*, the following: Sensation of hunger, languor, weakness; pallor or flushing of face, perspiration; glazed or masklike facies; numbness, tingling or other paresthesias in limbs or lips; diplopia, nystagmus, tendency of pupils to dilate, tinnitus aurium, dysarthria, dysphagia; motor weakness, hemiparesis,* incoördination, changes in reflexes, twitchings, convulsions, coma; psychic manifestations, as disorientation, confusion, emotional instability, delusions, obsessions, hallucinations, maniacal outbursts; aphasia, motor or sensory; total or partial amnesia of the reaction; inconstant changes in pulse rate, heart action, blood pressure and temperature. At the risk of repetition, it should be said that this list of signs and symptoms is given only as a summary of all those seen by various authors on different patients and that these actually never occur all together, but usually come only a few at a time during a given insulin reaction in a given patient. That these symptoms and signs are indicative of some involvement, though temporary, of the central or peripheral nervous system is obvious; this, in fact, was the impression gained by the earliest observers, Fletcher and Campbell,[2] in the first careful clinical study of insulin reactions. It should not then seem surprising that at times during an insulin reaction there may occur a train

* The hemiparesis is taken from a recently reported case of Miller and Thresher.[34]

of symptoms and signs of a more definite neurologic entity which may even be localizable in the central nervous system, akin to that encountered in a cerebral hemorrhage, embolism, or softening. This, in fact, is what the writer had observed on *two* (or *three?*) different occasions in one diabetic patient under his care. In this patient within a period of ten days there occurred during the course of two insulin reactions what appeared to bear all the earmarks of a typical complete hemiplegia and which cleared up completely after three and seven hours respectively.

No mention of such a manifestation of insulin hypoglycemia could be found in the literature.* Campbell and Joslin, however (in personal communications to writer) have each seen such a transient hemiplegia on two occasions, but never reported them. Joslin's cases, however, "were not so very transient," as in one of these the paralysis lasted a few days and in the other a few weeks. F. M. Allen (also in a personal communication) has seen "attacks like transient hemiplegias" in one patient at the Physiatric Institute. All three, however, agree that it is rather an unusual and rare manifestation of insulin hypoglycemia. It is because of this, and because of the new angle of approach, that it lends to the study and understanding of transient paralyses in general and to the mechanism of insulin action in particular, that the writer deemed it worth while to report this observation.

Parenthetically it may be mentioned that many more cases simulating a hemiplegia or other neurologic syndromes could be encountered with greater frequency in insulin hypoglycemias, were a more thorough and accurate neurologic examination made feasible. Thus, for example, in 1 of his 4 interesting cases of insulin reactions, Labbé[3] describes "shivering, perspiration, loss of consciousness, convulsions *with conjugate deviations of eyes and head to right* (italics are mine—J. M. R.), contraction of muscles of lip, cyanosis of face"—symptoms and signs which are indicative of a definite cerebral involvement. He makes, however, no mention of condition of limbs, reflexes, pathologic or otherwise, muscle tone and so forth. These simple observations might have helped in making the neurologic signs more of an entity and thus another interesting *transitory* paralysis would have been added on record. Numerous similar examples can be cited from the literature. But, while in the above case we can

* After this paper was completed, there appeared an article by Ashe, Mosenthal and Ginsberg[49] in which the authors mentioned the occurrence of an incomplete left hemiplegia in 1 of their 3 cases. The patient, a woman aged sixty-five years with diabetes mellitus and gangrene of the left foot, who was receiving only 5 units of insulin t.i.d., one day "suddenly became comatose, developed a right facial paralysis and left hemiplegia and stertorous respiration." The blood sugar at that time was 0.027 per cent. Glucose by mouth and intravenously brought a recovery. No detailed neurologic examination, however, is given by the authors. There may, of course, be other such isolated cases mentioned in the literature, but so far this is the only one instance that we could find.

understand that no time for a complete neurologic examination could be spent with the patient in coma, in other similar reports the incompleteness of observations can be explained by the fact that the average observer is satisfied by recording the more spectacular and obvious things, such as facies, mental reaction, diplopia, perspiration, and so forth, and he does not find it necessary to do a neurologic status. Thus, many interesting facts occurring in insulin reactions are lost to us. We have emphasized this point and laid so much stress on the great value of the study of all manifestations of insulin reactions with especial reference to their neurologic aspect, as, aside from furnishing us more information on the action of insulin, it may also shed some new light on the etiology and pathogenesis of organic and "functional" nervous diseases in general.

Report of Case. *History.*—The patient, C. B. L. (No. 175099), a young man aged thirty-four years, American, laborer, was admitted to the University Hospital on July 18, 1927, with the chief complaint of polydypsia, polyphagia, weakness, and loss of weight. He traces his present illness to five years before admission (29 aet.) when he began feeling "weak and lazy;" glycosuria was then discovered. For about four years afterward he was on a diabetic diet and got along fairly well. But seven months prior to admission he broke his diet and had been having all the classical symptoms of polyphagia, polydypsia ("1½ gallons of water a day"), polyuria, undue fatigability and loss of weight. In April, 1927, following a "bad cold" he had an episode of acidosis from which he recovered with the aid of insulin. Since then he required insulin daily. He gives also a history of diarrhea of a few months' duration. Review of other systems reveals nothing abnormal.

His *past history*, save for measles and influenza, carious teeth, head colds in the winter, is essentially negative. The *family history* is unimportant.

On *physical examination*, the patient was found to be a fairly well-developed undernourished man of thirty-four years (height, 160 cm.; weight, 44.2 kg.). Mucous membranes were of good color. The teeth were carious and pyorrhea alveolaris and gingivitis were marked. The tonsils were considerably enlarged and somewhat injected. A small adenoma was palpable in the left lobe of the thyroid. No signs of hyperthyroidism could be elicited. Examination of fundi showed a slight degree of neuroretinitis and a very small absorbed hemorrhage in right retina. There were also incipient lenticular opacities in both eyes. Lungs were clear. Heart appeared normal in size and shape; maximum right measured 3.5 cm. and maximum left 9.5 cm. in fifth interspace. Retromanubrial dullness was not made out. Radial and apex rates were 82 to 84 and with no deficit or arrhythmia. Peripheral arteries were not thickened. Blood pressure ranged between 110 to 118 systolic and 70 to 80 diastolic. Genitalia and rectum were normal. Neurologic examination revealed nothing abnormal.

Laboratory Findings. Urinalysis, except for high specific gravity and glycosuria, was negative. The *blood* showed hemoglobin, 80 per cent; red blood cells 4,200,000; white blood cells, 8500; differential count within normal limits. Roentgenographic studies of chest showed heart and lungs to be normal, and those of the gastrointestinal tract were suggestive of an ulcerative colitis. Basal metabolism rates ranged from +5 to +10. Glucose tolerance curve was typically diabetic.

Progress. We cannot go into details as to the dietetic and insulin regulation of this case, which presented a very interesting and difficult problem in itself, but which has no direct bearing on our present topic. In a general way it may be said that for a long time the patient showed a persistent glycosuria in the 6 and 9 A.M. fractional specimens even on insulin dosage of as high as 75 units per day and at the same time would frequently have insulin reactions in the afternoon between 3 and 9 P.M. This difficulty was finally solved by adjusting the insulin time in such a way as to combat the hyperglycemia and glycosuria at a time when they reached their peak. This was accomplished by dividing the morning dose of 30 units into two, one at 1.30 A.M. and the other at 7.30 A.M. The diet reached at the end consisted of: Protein, 60 gm.; fat, 280 gm.; carbohydrate, 65 gm., with total calories of 3000 and total available glucose of 126 gm. But before this was accomplished the patient had been having quite a few insulin reactions. (Seven in number from August 21 to August 27, and on this last date the morning urine contained 11.2 gm. of sugar!) Between August 31 and September 7 he had three remarkable reactions, the two last ones of which constitute the subject of our paper.

On August 31, 1927, *at* 6 P.M. (the following is almost an exact copy of the bedside notes) the patient was seen sitting in the solarium, smoking his pipe and appearing to be in good humor. Only when asked how he felt he replied that he was beginning to get numb over the right side of his body. On a cursory examination, response to a pin prick was markedly weaker over the right arm, right leg and to a less extent over the right half of the face. The right arm was flaccid and when raised passively would fall down lifeless. Motion was markedly diminished on the right arm and leg. Tone and motion in the left arm and leg were normal. Deep reflexes in right upper extremity were weaker than in the left one; deep reflexes in both lower extremities were markedly hyperactive. Pathologic reflexes were not tested. Speech was somewhat drawling. The patient was then ordered to bed, but as he could not walk by himself he had to be helped along. It was then observed that he supported himself on the left side, while his right arm hung lifeless at the side of the body and he was dragging along his right leg. His gait and attitude were typical of a hemiplegia. When put to bed he felt much better, smiled and claimed that his "reaction was over." Save for this flaccidity and loss of tone and motor power in the right arm and leg and drawling speech, he had no symptoms—not even any of the signs of his previous milder reactions—no sweating, diplopia or peculiar facies. No other examinations outside of those mentioned above were done at that time. The possibility of a hemiplegia following insulin was never heard of nor was it suspected, hence examination was not directed from this point of view. Patient said that he felt perfectly well, so he was left alone. It would be of interest before going to the description of the hemiplegias to tell what happened with the patient later in the evening, as it exhibits a few very interesting features of insulin reaction. At 8 P.M., or about an hour after he was left alone, when it was thought that he recovered from his reaction, the writer was summoned to see patient again. At that time one glance made it clear that he was in a deep state of insulin hypoglycemia. He lay motionless on the bed covers with a glazed expression to his face, eyes deviated to the left and the entire body was bathed in sweat. The extremities were held rigid, all deep reflexes, on hasty examination, were hyperactive, and considerable power had to be used in overcoming the rigidity of the arm for the taking of blood pressure and withdrawing some blood. Adrenalin ♏. x, and 200 cc. orange juice were given immediately. Within twenty minutes complete recovery ensued. Blood pressure taken before adrenalin injection was 150 systolic and 80 diastolic. This systolic was the highest ever observed in this patient, as it had been ranging between

110 to 120.* A blood specimen taken at 8.05 P.M. contained 0.015 per cent reducible sugar.† (For blood sugars, urine sugars and insulin dosages on the day of this and of the two other reactions, see table.)

On September 5 at 4.45 P.M. patient complained of numbness and tingling over the left side of body, left arm and leg and both sides of lower jaw, but none over lips and right side of body. He lay in bed with a somewhat vacant expression, was not perspiring and was mentally clear. When seeing writer at a distance he raised two fingers, meaning "I see double." His speech was weak and drawling. There was a marked asymmetry of face, left nasolabial fold and other wrinkles on this side were smoothened out. Left palpebral fissure was wider than right, and left side of face very weak, but forehead could be wrinkled very well and no asymmetry could be noticed on doing so. Left eye would not close as tight as right one. Left corneal reflex was diminished. Position of tongue was not tested. Left arm and leg were flaccid. He moved the left leg only slightly and very clumsily, but left arm and left hand he could not move at all. Knee jerks and Achilles jerks were undiminished on the affected side, but biceps and triceps jerks could not be obtained on that side. There was a marked hypalgesia to pin prick over left upper and lower extremities, and over left half of thorax and abdomen—over the latter it was patchy in distribution. There was no loss of sense of posture over affected side. A *positive Babinski* was obtained on left side—in marked contrast to the normal plantar flexion of the right toe. Confirmatories were not tested. Left *abdominal* reflex was *absent*—right abdominal was lively. A positive Raimiste's "sign of the hand" was also present on the right side, but there was no Klippel-Weil. *Blood pressure*—right arm was 108 systolic and 68 diastolic; left arm was 100 systolic and 68 diastolic. Pulse rate, 120. Heart was somewhat overactive, but no murmurs or arrhythmias were detected. Surface temperature of left side of body was higher than on right side. *Blood* taken at 5 P.M. showed 0.025 per cent sugar.

It was obvious then that patient presented the classical signs of a complete left hemiplegia akin to that seen in a lesion of the internal capsule. But in spite of this his condition in general did not look to be alarming; he himself voiced afterward an opinion that "this was a mild reaction." As supper time was approaching he was given his meal instead of the usual treatment. He took his food very well, though at first he showed some difficulty in swallowing. Writer felt safe to leave patient to himself and even ventured an opinion that from the history of a similar attack two days previously, patient would most likely have a complete recovery from the hemiplegia. At 6.30 P.M. neurologic findings were the same as at 5 P.M. Babinski

* This definite increase in systolic pressure is very interesting. For the question of blood-pressure changes in insulin reactions is not yet settled. Jung and Auger,[20] working on animals, showed that insulin provokes a definite and progressive fall in blood pressure which reaches its maximum at the end of one to two hours and returns to normal after three to four hours. While Klemperer and Strisower[21] found no marked fall in blood pressure in diabetic patients with normal pressure, Harrop[25] found in his cases a rise of 20 to 30 mm. in systolic pressure in mild reactions and no rise or even a fall in blood pressure in the severer reactions and in insulin coma. He, however, quotes Wilder,[22] as stating that increase in blood pressure in insulin reactions is a constant phenomenon.

† This is the lowest blood sugar ever observed by us in this or in any other patient during an insulin reaction. Campbell[26] gives the lowest figure in his cases as 0.025 per cent. The lowest blood-sugar figure ever reported in an insulin reaction is that by Smith,[23] in a boy aged four years, in whom no reducible sugar could be detected by the Folin and Wu method, so that "the blood was zero." It should be noted that in our patient even during a mild reaction the blood sugar would be as low as 0.03 per cent. Blood-sugar determinations were done according to the well-known method of Folin and Wu.

was still strongly positive on left side, left abdominal reflex was still absent and no tone or power had returned as yet to left side. He was then given adrenalin ♏. x, and 100 cc. of orange juice.

At 9 P.M. patient looked and felt well. He began showing first signs of recovery from his paralysis—the numbness in left arm and leg disappeared, the facial asymmetry was almost entirely gone, speech became clearer, motion returned to the left leg, but he could still not move the left arm or hand, and the left abdominal reflex became faintly perceptible. The remarkable thing then was that the left *Babinski* which only fifteen minutes before (at 8.45 P.M., and the patient was under constant observation) was strongly and unequivocally *positive* became now *negative*. By 11.45 P.M. he had completely recovered from his hemiplegia. His tone and motor power returned to the paralyzed left arm, left grip became as strong as the right one, Raimiste's sign of the hand was negative and power in the left leg and foot was as good as in the right one. Babinski in left foot was negative and left *abdominal* reflex was as lively as right one. Patient had full recollection of all that happened to him during the reaction. He got up and walked to the bath room, all smiles. Duration of this hemiplegia then was about seven hours. (For insulin dosage, urine and blood sugars of same day see table below.)

Two days later on September 7, 1927, there was a recurrence of a hemiplegic episode on the left side. And, although it exhibited almost the same features as on September 5, but because of the rarity of this condition in general it will be described here as well.

TABLE OF BLOOD SUGAR, URINE SUGAR AND DIACETIC ACID ESTIMATIONS: INSULIN DOSAGES.

		Urine specimens.								Insulin units.				Blood sugar, per cent.
		9 A.M.	12 M.	3 P.M.	6 P.M.	9 P.M.	12 P.M.	3 A.M.	6 A.M.	7.30 A.M.	12 M.	5 P.M.	Total.	
Aug. 31	Sugar	++++	++++	+	0	..	..	..	0	24	24	24	72	0.015 (8.05 P.M.)
	Diac.	+	0	0	0	..	..	..	0					
Sept. 5	Sugar	++++	+	Tr.	..	0	..	..	Tr.	33	10	15	58	0.025 (5 P.M.)
	Diac.	++	+	0	..	0	..	..	0					
Sept. 7	Sugar	++++	+	0	0	0	..	..	0	6 A.M. 33	10	10	53	0.028 (4.50 P.M.).
	Diac.	++	+	0	0	0			0					

At 4.35 P.M. patient began complaining of numbness, and his face took on that peculiar glazed appearance. *Blood* taken at 4.50 P.M. showed 0.028 per cent of reducible sugar. Supper was served to him at 4.55 P.M. He then looked and felt better. At 6.30 P.M. he seemed to grow worse. Flaccid paralysis began setting in in left arm and leg, same as was described on September 5. *Neurologic* examination revealed the following: *Cranial* nerves, pupils, both irregular, right medium-sized, left one olive-shaped, with the long axis parallel to bridge of nose. Reaction to light and accommodation, both directly and consensually, was fairly good in both. Left palpebral fissure was definitely wider than right one. Both corneal reflexes were weak, left more than right. There was a definite facial asymmetry with smoothening out of wrinkles of left side of face and around left eye. Left angle of mouth hung lower than right. On closing eyes there were wrinkles around right eye only. Motion of right half of face was markedly better. Same seen on smiling; right half of face smiled alone. "Smoke blowing" from left corner of mouth was very weak and clumsy. Forehead

could be wrinkled well on both sides. *Motor* power almost entirely lost in left arm, hand and leg, movement of left toes was almost imperceptible. *Tone*, flaccidity upper and lower left extremities. *Sensory* examination, marked hypalgesia and hypasthesia over left arm, hand, leg, foot and to a lesser degree over left half of face. There was also impairment of stereognosis in left hand. Vibratory sense was not tested. *Reflexes*, triceps, biceps, periosteoradial and knee jerk on left side were weaker than on the right. A *positive Babinski* was obtained on the left side. Oppenheim and Gordon reflexes were negative on same side. Other confirmatories were not tested for. A positive Raimiste's "sign of the hand" was present in the left hand, but no Klippel-Weil. Patient's mentality was clear, his speech was somewhat drawling.

Adrenaline ♏. x was given at 7.45 P.M. At 9.10 P.M. there was a complete recovery from all above-mentioned signs. Power, tone and motion were very good and same as on right side, facial asymmetry and weakness were gone; sensory changes were no more to be made out. *Abdominals* were equally *lively* on both sides and *Babinski* and *Raimiste* were *negative* on left side as well. Patient spent a good night and no residuum of the hemiplegia could be detected the following morning. He remembered all that happened to him during the reaction.* This then was the *second* (or *third?*) observed transient hemiplegic paralysis following insulin administration which at this time lasted only for about three hours. The signs were almost exactly as those seen in a lesion in the internal capsule.

For the sake of completeness it must be added that patient's remaining six weeks in the hospital were essentially uneventful. A thorough study of his blood and urine sugar at three-hour intervals day and night were made and insulin dosage and time so arranged that he had no more insulin reactions and remained more or less sugar-free during his remaining stay at the Hospital. On October 7 he had his tonsils removed and made an uneventful recovery from the operation. He was discharged home on October 20, 1927 with his diabetes more or less in control. Upon the day of his discharge he was given a thorough neurologic examination by Dr. R. L. Glass, of the neurologic department, and by the writer and no residua of the hemiplegia could be found. Through the courtesy and coöperation of the social service department of the hospital it was made possible to have the patient return to the hospital after four weeks for another examination. He appeared to have gained 8 pounds in weight during that month, looked and felt well. He had no insulin reactions and had been decreasing gradually the insulin dosage himself. On examination nothing new was found except for ophthalmoscopic findings. This time there was noticed a marked progression of the retinal involvement in form of numerous small hemorrhages in both fundi. These, according to Dr. G. Slocum, of the ophthalmology department, while not typical for diabetes could still be explained on this basis.

Discussion. We have described here, then, at least two episodes of a typical complete hemiplegia in a diabetic patient following insulin administration, both of which were transient in character, one having lasted seven hours, the other three hours, without either leaving residua after their disappearance. In their signs and symptoms these hemiplegias resembled very closely the picture seen in a lesion of the internal capsule. It is of importance to note that arteriosclerosis and cardiorenal disease can be excluded with reasonable certainty in this patient.

* Total or partial amnesia of the happenings during insulin reactions has been the experience of many observers. In our patient this did not seem to be the case.

Let us now consider the nature of this hemiplegia and the mechanism of central nervous system manifestations of insulin reactions in general. The first question we have to ask ourselves is the following: Is there an organic basis for these neurologic signs and symptoms, or would these have to be put in a class of, what, for lack of a better term, we may call, the nonorganic or *functional* phenomena, or, as Oppenheim would speak of them, as those *sine materia?* Let us then first turn to the literature for help in the solution of this problem and see whether we can find authentic cases wherein insulin has been proven to cause an organic lesion in the central nervous system or in any other system of the body. And with respect to this we may say in advance that there is not an abundance of material to consult—and this in spite of the universal use and abuse of insulin for the past five years. There are, it is true, some reports of deaths following insulin administration and Campbell[4] in the excellent monograph "Insulin," tells of 2 such cases. Deaths after insulin administration were also reported by Beck[5] and Heiman-Trosien and Kaufman.[6] The writer knows also of 1 case, a patient of Dr. Newburgh's service, who died suddenly a few weeks after her discharge from the hospital, and about whom there is also a strong suspicion that insulin precipitated her death. But as in none of the above cases was there postmortem examination performed, and also as no blood-sugar determinations were done in either of them, these cases cannot help us much in our problem. Ehrman and Jacoby,[7] however, did report 2 cases, "Hemorrhage Especially in the Lungs and Brain after Insulin," but this article is not at all convincing as to the direct specific effect of insulin in the described organic lesions. For both cases were in coma and insulin had no effect on it, as in both of these there was a constant *hyperglycemia* and blood sugar even immediately before death was never lower than 0.4 per cent. Furthermore, both showed a parenchymatous nephritis and in 1 of them there were also hemorrhages in the mucous membranes of the stomach and trachea so that, in the authors' own words, patients "were in coma which could not be saved by insulin," as "there was already a previous injury to bloodvessels." Therefore, while we cannot exclude the probability of insulin serving as contributory factor at least in these hemorrhages, the possibility of its playing a direct specific rôle in them is much in doubt. Güdemann[8] and Henderson[9] report 5 cases of hematuria and Güdemann also 2 cases of melena following insulin. But 2 out of the 5 were in coma, and the microscopic red blood cells found in their urines were accompanied by casts and albumin, which is not an uncommon finding in diabetic coma in general. Hence this "hematuria" loses somewhat in its importance. As in the remaining cases no hypoglycemic symptoms were present, and no blood-sugar determinations are given by the authors, the importance of the hematuria and melena is difficult to evaluate. For in

insulin treatment, the same as with any other drug, such as digitalis, for example, in order to attribute any untoward or toxic effects to it directly in a given case one should be able to demonstrate also its specific physiologic effects in that case. Thus, the criterion for determining whether a "reaction" following insulin administration is really an *insulin* reaction—a manifestation of its physiologic overactivity—there must be present at least one of the well-known symptoms of clinical insulin overdosage, or, in the absence of this, which is rather rare, at least a lowered blood sugar must be demonstrated.* This view with regard to the hypoglycemia is also shared by W. R. Campbell,[10] who, in commenting on our case of transient hemiplegias, states that it is "essential to demonstrate the hypoglycemia by blood-sugar determinations, as these transient hemiplegias are not very uncommon in the elderly diabetics with arterial disease."

We see then that with a few rare instances—and in these the exact rôle that insulin plays has not been well established—no specific organic lesions have been found clinically in insulin hypoglycemic reactions. Experimentally, though, in animals Poll[18] and Kahn[19] have produced morphologic changes in the medulla of the adrenals and in the splanchnic nerve by "insulin poisoning." It remains then to look for the mechanism of nervous system involvement in insulin reactions, and in our case in the hemiplegia outside of the organic sphere and we shall then put this in the class of syndromes *sine materia*. This assumption, for the time being at least, seems to be the more plausible one. For, if there is one thing that is common to all insulin reactions, and which was the salient feature in our hemiplegia, it is their *transitory* character. Any symptoms or signs which clear up within a few hours, or even within a day or so, must needs be indicative of some *temporary* nonanatomical disturbance rather than of one which is organic and, therefore, more or less permanent.

Transient and periodic paralyses which could not be explained on a basis of actual damage to the nervous system are in general not infrequent in the annals of neurology. This is especially true with regard to transitory hemiplegias. Bastian,[11] in 1875, in his classical lectures at the University College, London, was the first to call attention to this fact. He would, only "for the sake of brevity," class such hemiplegias under the heading of "spasms of vessels," although he, himself, did not think that this could explain all such

* With regard to the last point, it must be mentioned that only occasionally do we meet with cases who show symptoms simulating insulin hypoglycemia in which blood sugar is even above 0.11 per cent. Such cases have been reported by Campbell,[26] Harrop[25] and John.[27] The latter found 5 such cases with blood sugar of over 0.2 per cent. We cannot go into the discussion as to these exceptions at the present time. Furthermore, hypoglycemia *per se* cannot always be looked upon as the result of insulin overdosage alone, for this can be met with in the so-called spontaneous hypoglycemia, starvation hypoglycemia, and may be even found in normal individuals as was found by Gray.

temporary and transitory paralyses, but meant that causes akin to that of vessel spasm could account for them. Many cases have been reported since, especially in diabetes mellitus. Naunyn,[12] in 1890, cites such cases in diabetes. One of these, a diabetic woman, aged eighty-nine years, became suddenly comatose, and had right-sided hemiplegia involving right arm, leg, lower facial, with aphasia. On section the brain showed nothing, "not even arteriosclerosis." Oppenheim[13] has seen many such cases in diabetes, especially bulbar palsies, which cleared up entirely. Hemiplegias without anatomic changes in brain have also been described in other conditions, such as tuberculosis, alcoholism, uremia, pneumonia, arthritis and so forth. A very interesting case was recently described by Finesilver,[14] in an old woman with arteriosclerosis and Parkinsonism, who suddenly had a typical left hemiplegia with a left lower facial palsy and which lasted a very short while. The hemiplegia then, that we have observed on three occasions in one patient as a result of insulin treatment does not stand out as a syndrome which is extraordinary and *sui generis*, but is only another instance of the large class of the transitory hemiplegias in general.

When we come now, finally, to consider the exact mechanism of the action of insulin on the body tissue in general, and on the nervous system in particular, it must be admitted that we are still in the dark concerning it. Even the chemical-metabolic aspect of insulin action is not yet thoroughly understood. Many suggestions and theories have been advanced by such men as Geelmuyden, Biedel, Laufberger, Magnus-Lævy, Brugsch, Embden, Neuberg[15] and others with respect to this. Yet in the light of work of Brunt and Dale[16] and of Macleod[17] and his group it would seem that the immediate result of insulin action is to be found in the nonreducible, nonoxidizable intermediary carbohydrate products, and cannot be explained on the simple and universally used formula of glycogenesis *vs.* glycogenolysis. What these intermediary substances are is still unknown. Then, if with regard to the chemical-metabolic aspect of insulin action, upon which a tremendous amount of work has been done, there exists such uncertainty, no wonder that the physiologic side of insulin action on which much less work has been done is still more shrouded in mystery. Among the investigations and theories in the latter direction may be cited the following:

From the morphologic changes found in medulla of both adrenals in animals after insulin administration by Poll[18] and Kahn,[19] and from his observation that sectioning of the splanchnic nerve in the guinea pig protects this organ from such changes, Kahn[19] believes that the "effect of insulin poisoning on the adrenal of the guinea pig follows along the nerve paths." Insulin is thought by Citron,[20] Carrelon and Santenoise[21] to be a stimulant of the parasympathetic system, as it was found by them to have a very marked excitatory

effect on the vagus.* Houssay,[22] in summing up the pharmacologic interrelations of insulin and other substances, believes also the same, and concludes that in a general way the stimulators of the sympathetic system oppose insulin hypoglycemia, the inhibitors of the sympathetics augment it, and inversely the stimulators of the parasympathetics augment it.

Mueller, Wiener and Wiener,[23] on the basis of the marked difference in the effect of insulin when administered intradermally or otherwise tend also to the view that insulin acts mainly on the parasympathetic system. (Although their conclusion as far as it gives the main rôle of this nerve stimulation in increasing glycogen storage in the liver is, in the light of newer experiments of Brunt and Dale and of Macleod, not borne out.) Cannon, McIver and Bliss[24] consider hypoglycemic reactions in general as indications of "discharge of sympathetic impulses," and seem to have shown experimentally in animals with denervated hearts that adrenal secretion is involved in these reactions. Mueller and Petersen[25] would also include the vascular system in this scheme, believing that insulin shock is due to acute disturbance of autonomic nervous system which consists in predominance of sympathetics in tonus of bloodvessels of the splanchnic region (liver) and predominance of parasympathetics at the periphery. Nechkovitch,[26] in speaking of insulin convulsions, and on the basis of his work that *in vivo* and *in vitro* there is an antagonism between glucose and hydrogen ions, believes that these convulsions are provoked by "a change in colloidal state of nerve centers, which in turn is due to action of hydrogen ions and diminution of glucose." According to Krogh,[27] the "point of attack" of insulin is in the tissues themselves, so that by being given off in them, though in very minute amounts, insulin leads to the first alteration of sugar and thus creates in the tissues a "vacuum" for glucose. Macleod also thinks that one must imagine the cause of hypoglycemic reactions to be in the development of some toxic condition in the nerve cells, the prevention of which in the normal animal is dependent on a certain percentage of glucose in the tissue juices. Finally, from the work of Haldane,[28] Edwards[29] and Cannon, McIver and Bliss,[24] it appears that under insulin definite changes take place in the functional activities of the heart and in the circulation.

It is seen then from the above that the entire problem of the exact mechanism of insulin action from the metabolic as well as the physiologic aspects is far from being settled. It would, therefore, be impossible at the present time to postulate any definite and set theory as to the specific nature of insulin action on the nervous system. Suffice it to say, that it is our impression that, aside from all other effects, there is always a definite action of insulin on the

* Popper,[33] on the other hand, could not confirm vagus stimulation by insulin.

central and peripheral nervous systems. This action may be initiated directly by insulin itself or indirectly by the still unknown intermediary products of carbohydrate metabolism, as by creating, as it were, a "vacuum" for glucose in the nerve tissues. The resulting effect, then, may show itself by the alteration in function of either the nerve elements themselves or the bloodvessels supplying them.

Summary and Conclusions. 1. A new syndrome of a complete hemiplegia occurring on three different occasions in a diabetic during an insulin hypoglycemic reaction is described. Two of these hemiplegias exhibited the classical features of those seen in a lesion of the internal capsule and possibly also involving the retrolenticular portion of the posterior limb (the latter because of the marked hemianesthesia).

2. The hemiplegias were *transitory* in character, lasting three to seven hours, were followed by a complete recovery and left no residue of the paralysis after their disappearance.

3. It is of importance to note that in this case (a man aged thirty-four years) arteriosclerosis and cardiorenal disease can be excluded with reasonable certainty, and that at the same time, in all the three episodes of transient hemiplegias a definite *hypoglycemia* has been demonstrated (blood sugar ranging from 0.028 to 0.015 per cent).

4. It is noteworthy that in this case the hemiplegias were not commensurate with the degree of symptoms in general, that is, the entire *symptom* complex in the three reactions during which those hemiplegias occurred was comparatively mild in character.

5. It was shown that this new phenomenon of transient hypoglycemic hemiplegia is not a syndrome *sui generis*, but belongs to the rather general and not infrequently encountered group of transient paralyses and hemiplegias.

6. Views and experimental data regarding the mechanism and nature of the action of insulin from the chemical-metabolic and physiologic aspects were reviewed and discussed.

7. The assumption is made here that the nature of the central nervous system involvement in at least nonfatal insulin hypoglycemic reactions in general and in our hemiplegias in particular is "functional" or of *sine materia* character, implying by this that no actual anatomic lesion but only a temporary transitory disturbance is produced.

8. The idea put forward here is, that, aside from all other effects of insulin in the hypoglycemic reactions, there is always a definite action on the central or peripheral nervous system. This action may be initiated directly by insulin itself or by the still unknown intermediary products of carbohydrate metabolism that it produces, as by creating, as it were, a "vacuum" for glucose in the nerve tissues or by a process similar to this. The resulting effect,

then, may manifest itself by alteration of function of either the nerve elements themselves or the bloodvessels supplying them.

9. A summary of symptoms and signs occurring in insulin reactions in general is given.

NOTE.—My acknowledgment is due to Dr. L. H. Newburgh for privilege of reporting the case and for helpful criticism of the paper.

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SUPRARENAL INSUFFICIENCY: REPORT OF TWO CASES.

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Those who find an appeal in the history of medicine are always interested in the circumstances surrounding the origin of a disease that bears a man's name. They feel admiration for a man who possessed a keenness of perception, a shrewdness and sagaciousness which enabled him to correlate a group of symptoms with a definite entity which had previously been unrecognized, and having recognized this entity to delve into its depths and reveal the cause. This is especially true when the original description remains practically unchallenged after nearly seventy-five years.

In 1824, at the age of thirty-one, Thomas Addison was made

assistant physician in Guy's Hospital and at thirty-four he held the chair of materia medica. At that time students paid separate fees for courses of lectures; Addison's reputation as a practical teacher had spread so that his courses were keenly sought by the students. In 1837, he received the appointment of physician to the hospital and was at the same time selected as the colleague of Doctor Bright, in the chair of medicine. He had now achieved the desired position for the development or rather the demonstration of the qualities which he had so painstakingly cultivated, those of the eminently practical physician. Indeed, his strong, positive, and perpetual insistence on the term, practical, in reference to disease constitutes the key to Addison's character and his professional career. He was always ready to discuss newly started theories, but he never, for a moment, allowed them to interfere with the results of his matured experience.

It is refreshing in these days of mechanical diagnoses, to read of one who was able to correlate what he saw before him with what he had learned by reading and experience. Nothing is gained by looking at a thing if by so doing one is unable to interpret what is seen.

Wilks and Daldy illustrate many instances of Addison's positive personality. He never reasoned from a half-discovered fact but with dogged determination traced the disease to its very source, to the end that his class and his attendant friends were constantly wearied. If at last he could lay his finger on the disease, his victory was attained and his painstaking efforts satisfactorily rewarded. For with him, accurate diagnosis was the great, and too often the ultimate, object of an industry of search, a correlation of facts deduced from scientific observation and a concentration of thought rarely combined in the individual physician.

To those who knew him best, Addison's power of searching into the complex framework of the body and dragging the hidden malady to light, appeared unrivaled; but this one great object accomplished, did he devote the same energetic power to its alleviation or cure? Without accusing Addison of a meditated neglect of therapeutics, there is found evidence of dallying with remedies which has been characteristic of more recent times. Ambroise Paré in his "Journeys in Diverse Places" depicting his life as a surgeon following the armies, repeatedly remarks, "I dressed him and God healed him." So with Addison: "I have worked out the disease, if it be remediable, Nature with fair play, will remedy it. I do not clearly see my way to the direct agency of special medicaments but I must prescribe something for the patient, at least to satisfy his or her friends." This typifies a mind dealing with the observable and proven and shrinking from the uncertain and questionable.

Addison, in his original article, speaks of the paucity of knowledge concerning the suprarenal glands and the trepidation with which he

reveals his ideas and opinions lest they be thought hasty and overstated:

"Under the influence of these considerations I have for a considerable period withheld, and now venture to publish, the few facts bearing upon the subject that have fallen within my own knowledge, believing, as I now do, that these concurring facts, in relation to each other, are not merely casual coincidences, but are such as admit of a fair and logical inference—an inference that, where these concurring facts are observed, we may pronounce with considerable confidence the existence of diseased suprarenal capsules.

"As a preface to my subject, it may not be altogether without interest or unprofitable to give a brief narrative of the circumstances and observations by which I have been led to my present convictions.

"For a long period I had from time to time met with a very remarkable form of general anemia, occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood, no exhausting diarrhea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease.

"Accordingly, in speaking of this form in clinical lecture, I perhaps with little propriety applied to it the term 'idiopathic,' to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anemic state.

"The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same fatal result.

"It occurs in both sexes generally, but not exclusively, beyond the middle period of life, and, so far as I at present know chiefly in persons of a somewhat large and bulky frame, and with a strongly-marked tendency to the formation of fat.

"It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse, perhaps, large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some slight edema is probably perceived about the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness

of, perhaps, several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.

"With perhaps a single exception the disease, in my own experience, resisted all remedial efforts, and sooner or later terminated fatally.

"On examining the bodies of such patients after death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences; nevertheless, from the disease having uniformly occurred in fat people, I was naturally led to entertain a suspicion that some form of fatty degeneration might have a share, at least, in its production; and I may observe that, in the case last examined, the heart had undergone such a change, and that a portion of the semilunar ganglion and solar plexus, on being subjected to microscopic examination, was pronounced by Mr. Quekett to have passed into a corresponding condition.

"Whether any or all of these morbid changes are essentially concerned—as I believe they are—in giving rise to this very remarkable disease, future observation will probably decide.

"The cases having occurred prior to the publication of Dr. Bennett's interesting essay on 'Leucocythemia,' it was not determined by microscopic examination whether there did or did not exist an excess of white corpuscles in the blood of such patients.

"It was while seeking in vain to throw some additional light upon this form of anemia that I stumbled upon the curious facts which it is my more immediate object to make known to the profession; and however unimportant or unsatisfactory they may at first sight appear, I cannot but indulge the hope that, by attracting the attention and enlisting the coöperation of the profession at large, they may lead to the subject being properly examined and sifted, and the inquiry so extended as to suggest, at least, some interesting physiologic speculation, if not still more important practical indications.

"The leading and characteristic features of the morbid state to which I would direct attention are, anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin, occurring in connection with a diseased condition of the 'supra-renal capsule.'"

Addison's discovery of the heretofore unsuspected disease of the suprarenal capsules was the result of an exhaustive analysis of every organ of the body, without elucidating any evident reason for a remarkable form of anemia. For a time he was constrained to the expression "idiopathic anemia," a condition accompanied by a fatal prognosis. This prognosis was so constantly verified that Addison observed an association between it and a peculiar appearance of the suprarenal capsules.

Today, there is the advantage of additional clinical facts. In his time, skin disease was confined to the province of the surgeon. Previous to Addison's association with Guy's Hospital, he was attached to the General Dispensary. At this time, he studied with the celebrated Bateman and he became so proficient in his knowledge of skin diseases that after the death of the great dermatologist, the crown fell on Addison. From his desire to avoid the pursuit of this specialty, his competency was not generally known, yet it is certain that for a long time Addison's accuracy in the discrimination of cutaneous eruptions was scarcely matched. It is probable that but for Addison's accurate observation of the various deviations of cutaneous conditions from the normal and healthy, the bronzed skin would not have riveted his attention so forcibly as to have incited him to trace its cause.

Addison's original description of the disease remains unchanged today with but one exception. He believed that an anemia was one of the outstanding features of the malady and he called it idiopathic anemia, previous to his discovery of suprarenal changes. This belief was undoubtedly based on the general appearance of the patients, as blood studies were probably not a means of diagnosis in Addison's time. Today, however, anemia is only rarely associated with Addison's disease.

All of Addison's original cases came to necropsy. He remarks: "With perhaps a single exception the disease, in my own experience, resisted all remedial efforts and sooner or later terminated fatally." He makes no further reference to this exceptional case.

Conybeare and Millis report 29 cases proved at necropsy to be Addison's disease, occurring between 1904 and 1923 at Guy's Hospital. They believe that it is almost impossible to be certain of the diagnosis until confirmation is made at necropsy. In a number of cases the condition was diagnosed Addison's disease during life, but at necropsy the diagnosis was disproved. Are we, then, to confine our diagnosis of Addison's disease to those cases presenting the characteristic symptoms and ending fatally? Is death necessary before a positive diagnosis is possible?

In a large majority of the cases ending fatally there is tuberculous destruction of the glands; in a certain percentage, however, there is simple atrophy.

Is it a fallacy to presume that functional dyscrasia of the suprarenal glands cannot exist? Other glands necessary to life are known to be so affected. Thyroid deficiency in the form of myxedema may, if untreated, lead to death, yet by compensating for this deficiency by administration of thyroid extract a condition of well-being may be maintained for years.

Is there, then, justification for making a diagnosis of Addison's disease in a person presenting the usual symptoms, if on substitutional treatment improvement occurs, and when a reversion to the

former state takes place on withdrawal of the treatment, or must this be called suprarenal insufficiency and the term, Addison's disease, be reserved for those cases which end in death and in which the pathologic observations establish this diagnosis?

"But," says Addison, "if the obscurity which at present so entirely conceals from us the uses of these organs (suprarenal) justifies the feeblest attempt to add to our scanty stock of knowledge, it is not less true, on the other hand, that any one presuming to make such an attempt ought to take care that he does not by hasty pretention or by partial or prejudiced observation, or by an overstatement of facts, incur the just rebuke of those possessing a sounder and more dispassionate judgment than himself."

Pigmentation of hands, arms, face and neck in Addison's disease.

Report of Cases. CASE I.—A man, aged forty-three years, came to the Jackson Clinic in the spring of 1920 complaining of a gradually increasing weakness, which after a month's duration necessitated his stopping work. Soon the fatigue, resulting from going out of doors, compelled him to remain in the house. The weakness became so discomforting that he had no desire to move about and was contented to remain in bed much of the time. Effort, besides being very tiring was associated with dyspnea, and slight dizziness. Within a short time after the onset of weakness the patient noticed that the skin of his hands, arms, and face was becoming darker. Coincidentally with the progression of the weakness there occurred an increase in the pigmentation of the skin. He lost his appetite, but at no time was there vomiting or other digestive disturbances. He had lost 11 pounds.

At the time of the patient's examination, about a month after he had stopped work, there was a peculiar and decided pigmentation of the hands, arms, face, and neck which approximated the natural hue of a mulatto

(see illustration). The color was a blackish brown; on close inspection it was mottled rather than evenly distributed. The hands and arms were affected as far as just above the elbows and besides the face and neck the remainder of the body was not pigmented. There was no definite discoloration about the axilla or genitalia, nor was any pigmentation of the tongue discernible.

The systolic blood pressure was 104, the diastolic 70, and the pulse rate was 60. The hemoglobin was 85 per cent, the erythrocytes numbered 4,400,000, and the leukocytes 10,000. The urine contained a small amount of albumin and a few pus cells. The blood Wassermann reaction was negative.

Because of the asthenia, pigmentation, and low blood pressure, a diagnosis of Addison's disease was considered and substitutional treatment instituted: 5 gr. of suprarenal extract was given three times daily.

In three weeks the patient returned, stating that he was feeling stronger, did not tire as readily and felt that before long he could resume his work. He had noticed that his skin was somewhat lighter. He continued to gain in strength, and soon was able to take up his former work without tiring. A year later he was feeling as well as ever. The systolic blood pressure was 114 and the diastolic 64. His skin was much lighter but was still darker than normal. He had found it necessary to take one tablet of the extract a day; when this was omitted for a few days he began to notice loss of strength and lassitude.

The patient has been under constant observation for seven years. During this time he has taken suprarenal extract almost continuously. He has tried at various times to do without it, but on each occasion after a period of a week or ten days, he noticed such a change manifested by a diminution in ambition and strength that it was necessary to resume the extract. At the present time he takes 10 gr. at bedtime. The systolic blood pressure is 118 and the diastolic 80. The skin which was affected is still darker than normal, although it is considerably lighter than it was at the onset of the disease. His strength is normal and he feels quite well.

Comment. This case presents the triad of severe asthenia, discoloration of the skin, and low blood pressure, clinically Addison's disease. On specific treatment, there was an amelioration of all symptoms and restoration to normal health as long as treatment was continued. This has been maintained for seven years. Whenever treatment was discontinued there was evidence of reversion to the former pathologic state, and this again was checked when treatment was resumed. Such a course points to a deficiency in the normal production of suprarenal secretion which is compensated for by artificial administration.

CASE II.—A girl, aged nineteen years, first came to the clinic in 1906. As a child, she had been subject to attacks of headache and vomiting which lasted until she was about twelve years of age. At the age of eight years her skin which previously had been clear, had begun to grow dark. This had been especially noticeable on the forehead and later on the abdomen. Three years later the ankles and feet had become swollen. Exercise of any degree was extremely fatiguing and she had been unable to run and play with the other children. During the succeeding eight years there had been a gradual but progressive increase in the swelling, and it had extended as far as the knees. The hands and face had also become swollen. The entire body had become darker. Her menstrual periods began when she was

seventeen and then occurred about every three months. There would be a profuse flow for one or two weeks, necessitating the patient's staying in bed. At the time of her coming to the clinic, the weakness had become so profound that it was necessary for her to be brought on a cot. Walking was provocative of great weakness and dyspnea.

On examination a myxedema-like swelling of the lower legs, feet, face, and hands was noted. The entire skin was bronzed. This was most noticeable on the exposed surfaces, especially on the forehead. Her appearance was likened to that of an Indian squaw.

No determination of blood pressure was made. The condition was considered to be Addison's disease with myxedema.

The patient was given 5 gr. of thyroid extract three times a day, and 3 gr. of suprarenal extract, five times a day. In three months the edema had completely disappeared. There was a marked increase in strength and a decided fading of the bronzed hue of the skin. Her general condition continued to improve until soon she considered herself normal, although it had been so many years since she had been well that she scarcely felt in a position to make the judgment.

For many years, this patient has been taking both thyroid and suprarenal extracts daily. Her recent method of taking them is best expressed in her own words: "I have learned to know when I need them. The best test is for me to go up a flight of stairs. If the muscles in my lower limbs feel strained or I feel out of breath or exhausted, I know I need to take the thyroid tablets. When someone remarks about my complexion looking dark, I know I need to take suprarenal tablets." If the suprarenal extract is discontinued for several months, the skin becomes brown but it fades soon after the extract is again taken. She considers her health at the present time better than the average. In the twenty-one years, she was incapacitated only four days when she was ill with influenza, and a part of a week on two different occasions when she was operated on for hemorrhoids.

In 1920, the systolic blood pressure was 112 and the diastolic 86. The urinalysis was negative. The blood chemistry determinations were: blood sugar 98.5 mg. for each 100 cc. of blood; urea, 58 mg.; urea nitrogen, 26.5 mg.; creatinin, 1.66 mg.; chlorides, 0.6 for each 100 cc. of plasma. Gastric analysis revealed a total acidity of 26, 38 and 40, and free hydrochloric of 16, 20 and 22 after forty-five mintues, one hour, and an hour and a quarter, respectively.

In February, 1927, the systolic blood pressure was 120 and the diastolic 86.

Comment. This case presents the syndrome of hypofunction of both the suprarenal and thyroid glands. When the thyroid extract is omitted, the edema tends to recur; when the suprarenal extract is omitted the skin becomes darker; both conditions disappear when the extracts are again administered.

In some cases of myxedema, the thyroid gland may be completely atrophied. In the majority of cases which have come to necropsy, the gland has been found to be sclerotic, fibrous and hard. Notwithstanding the presence of such a pathologic condition patients may live for many years by taking thyroid extract.

Cases of apparently true Addison's disease have been reported when the suprarenals on postmortem examination showed simple atrophy instead of the usual fibrocaseous tuberculous changes. In other instances the suprarenals have appeared normal; that is, the

function may have been interfered with by some depressing nervous factors involving the solar plexus and semilunar ganglia.

If the administration of thyroid extract can maintain life and health in the presence of atrophy or sclerosis of the thyroid gland, as much might be expected following the administration of suprarenal extract in those cases of dysfunction of the suprarenal glands in which there is no morbid pathologic process or perhaps only simple atrophy.

Summary. A biographical sketch of Addison is given and a survey of his investigation of the disease which bears his name.

Two cases are presented which clinically conform to Addison's disease. Both patients improved under substitutional therapy and are still living. Both had recurrence of symptoms whenever treatment was discontinued.

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THE BLOOD PRESSURE IN PERNICIOUS ANEMIA.

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It is commonly recognized that the blood pressure is low in pernicious anemia but search of the literature fails to disclose any adequate statistical study of the subject. Cabot, in Osler's System,[1] states that "the blood pressure is very low," and that "readings of 60 to 80 mm. of Hg. for the systolic pressure . . . are not unusual." The only statement regarding blood pressure in Minot's Oxford Medicine[2] article on pernicious anemia is "the blood pressure is usually low." In a recent paper, Minot and Murphy[3] state that the blood pressure in pernicious anemia is apt to be relatively low. They also make the observation that 3 patients out of 105 had hypertension before the onset of anemia. In his very complete monograph, Friedlander,[4] in discussing hypotension in pernicious anemia, cites Cabot only. Sheard[5] found a persistently low blood pressure, both systolic and diastolic, in all but 1 of his 15 cases. This patient, who was excitable and experiencing psychic disturbances, had a persistently high systolic pressure only. Giffin and

Bowler[6] state that hypotension is characteristic of most patients with pernicious anemia—the diastolic as well as the systolic being distinctly below normal. In addition, they found that 4 of their 628 patients (0.64 per cent) showed hypertension. Gulland and Goodall[7] state that the pulse in pernicious anemia is of small volume and low pressure. They also speak of 2 patients with systolic pressure of 180 and 220 mm., who showed a drop to 140 and 160 mm. respectively at the onset of pernicious anemia. The only statistical data we have found on the blood pressure in pernicious anemia is that of Wilson and Evans.[8] It shows the distribution of the systolic pressure only of 111 cases for all ages. Nine of their patients (8.1 per cent) had a systolic pressure below 100 mm., and 17 (15.3 per cent), 140 mm. and over. They further state that 16 cases (14.4 per cent) had a pulse pressure below 40 mm. and 15 (13.5 per cent) over 70 mm.

In searching for material in the literature with which to compare our results, we were surprised to find a lack of statistical data on the distribution of blood pressure in the general population. Most studies are based either on limited age groups or on selected cases. The former objection applies to an excellent monograph on blood pressure by Stocks and Karn;[9] the latter applies to the mass of statistics based on life insurance examinations, as has been repeatedly pointed out by Alvarez, who has contributed several excellent statistical studies on the blood pressure of his private patients.[10] However, we cannot use his figures, first, because they are based on patients, and second, because these patients are members of the upper and middle classes of society. That social condition is a factor in determining the blood-pressure level is indicated by the studies of Stocks and Karn.[9] Another extensive study of blood pressure is that of Dunham,[11] based on the examination of 8645 army officers in 1924. But in this instance also, all those showing evidence of disease which might affect the blood pressure were excluded. Table I is a summary of the blood-pressure averages found by Alvarez,[10] Dunham[11] and Symonds,[12] and indicates that Dunham's figures are similar to those of the life insurance company; whereas Alvarez' figures are much higher, especially for the older age groups. In spite of the objections to the life insurance figures, we shall employ them below for purposes of comparison, for, in this particular study, they serve our purpose better than any others available.

Method and Material. Our study is based on the blood-pressure findings in 500 consecutive cases of pernicious anemia.* A few cases were discarded because no blood pressure had been recorded. When several readings had been made in any case we averaged them.

* Four hundred and thirteen cases were from the Massachusetts General Hospital and 87 from the Peter Bent Brigham Hospital. We are grateful to the latter institution for permission to use its data. The former include all the cases of pernicious anemia seen during the interval from 1914 to the middle of 1927, and the latter from 1924 to 1926 inclusive.

Unfortunately in many instances a single reading only of systolic and diastolic pressure had been taken, usually on the day of entry to the hospital. The observations were all made with the patient in bed by the auscultatory method of Korotkoff.

TABLE I.—AVERAGE BLOOD PRESSURE (MM. OF HG.): COMPARISON OF RESULTS OF THREE INVESTIGATORS.

	Male.		Female.	
	Systolic.	Diastolic.	Systolic.	Diastolic.
15 to 29 years:				
Alvarez	129.4	....	126.3	83.7
Dunham	122.0	76.0		
Symonds	123.4	79.8	120.6	78.4
30 to 39 years:				
Alvarez	130.5	....	129.8	86.1
Dunham	123.0	77.0		
Symonds	124.3	82.0	122.4	80.9
40 to 49 years:				
Alvarez	133.4	....	141.4	91.4
Dunham	127.0	81.0		
Symonds	127.3	84.3	126.9	84.1
50 to 59 years:				
Alvarez*	144.1	....	157.3	96.1
Symonds	131.6	86.5	132.1	87.3
60 years and over:				
Dunham†	134.0	83.0		
Symonds	135.2	86.6	135.5	89.8
All ages:				
Alvarez	134.7	....	137.6	87.9
Dunham	125.0	78.0		
Symonds	125.3	82.1	122.8	80.5

* Includes all cases over 50 years.
† Covers age group 50 to 64 years.

Results. In Tables II, III, IV and V, the readings for the systolic and diastolic pressures of 500 cases of pernicious anemia are analyzed according to age and sex. Here the means were calculated from the actual recorded pressures and not from the tabulated pressures, and their probable errors were determined roughly as the median error.[13] These figures, taken by themselves, show little variation due to age or sex, with the exception of female systolic pressures which show a definite upward trend with age.

Compared with the life insurance data of Symonds,* as in Fig. 1, they bring out several interesting facts. The means for both systolic and diastolic pressure of our series of cases are definitely lower than the corresponding ones of the accepted risks of the life insurance company; the diastolic means are relatively lower than the systolic means. The differences in the means are large enough to be very significant,† except for those age groups in which the number of

* We have been unable to find life insurance data for the "spread" of blood pressure; consequently we are obliged to compare the means only.

† The probable error of the life insurance figures is small. Their results are, therefore, reliable.

TABLE II.—DISTRIBUTION OF SYSTOLIC PRESSURE IN PERNICIOUS ANEMIA—MALES.

Pressure, mm. Hg.	Up to 29 years.		30 to 39 years.		40 to 49 years.		50 to 59 years.		60 to 69 years.		70 years and over.		All ages.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Up to 99	...	....	1	3.8	12	17.6	12	11.6	5	8.5	1	16.7	31	11.5
100 to 109	1	14.3	2	7.6	10	14.7	21	19.7	7	11.9	1	16.7	42	15.5
110 to 119	2	28.5	14	53.9	13	19.1	28	27.2	12	20.3	1	16.7	70	26.0
120 to 129	3	42.8	6	23.2	22	32.3	17	16.5	12	20.3	...	....	60	22.2
130 to 139	1	14.3	2	7.6	9	13.2	11	10.7	13	22.1	...	....	36	13.3
140 to 149	...	....	1	3.8	1	1.5	10	9.7	4	6.8	2	33.2	18	6.7
150 to 159	...	....	...	....	1	1.5	1	1.0	3	5.1	1	16.7	6	2.2
160 to 169	...	....	...	....	...	....	3	2.9	...	....	...	....	3	1.1
170 to 179	...	....	...	....	...	....	...	....	2	3.4	...	....	2	0.7
180 to 189	...	....	...	....	...	....	...	....	1	1.7	...	....	1	0.4
Total	7		26		68		103		59		6		269	
Mean	118.2 ± 1.9		116.4 ± 1.5		114.5 ± 1.4		117.3 ± 1.2		122.7 ± 1.4		122.5 ± 5.8		117.9 ± 0.66	

TABLE III.—DISTRIBUTION OF DIASTOLIC PRESSURE IN PERNICIOUS ANEMIA—MALES.

Pressure, mm. Hg.	Up to 29 years.		30 to 39 years.		40 to 49 years.		50 to 59 years.		60 to 69 years.		70 years and over.		All ages.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Up to 49	2	28.5	1	3.8	6	9.0	7	6.5	3	5.1	...	....	19	7.1
50 to 59	1	14.3	4	15.4	16	23.5	27	26.3	13	22.1	2	33.2	63	23.4
60 to 69	2	28.5	15	57.8	26	38.1	31	30.1	23	39.1	3	50.0	100	37.2
70 to 79	2	28.5	2	7.6	14	20.5	26	25.4	13	22.1	...	....	57	21.1
80 to 89	...	....	3	11.6	6	9.0	10	9.7	6	10.7	1	16.7	26	9.6
90 to 99	...	....	1	3.8	...	....	1	1.0	1	1.7	...	....	3	1.1
100 and over	...	....	...	....	...	....	1	1.0	...	....	...	....	1	0.4
Total	7		26		68		103		59		6		269	
Mean	59.5 ± 3.1		65.0 ± 1.7		62.8 ± 0.77		64.4 ± 0.84		64.4 ± 0.97		61.7 ± 1.0		63.9 ± 0.46	

TABLE IV.—DISTRIBUTION OF SYSTOLIC PRESSURE IN PERNICIOUS ANEMIA—FEMALES.

Pressure, mm. Hg.	Up to 29 years.		30 to 39 years.		40 to 49 years.		50 to 59 years.		60 to 69 years.		70 years and over.		All ages.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Up to 99	1	10.0	2	8.3	9	12.9	10	13.0	2	4.7	...	....	24	10.4
100 to 109	6	60.0	6	25.0	8	11.4	10	13.0	6	14.2	...	....	36	15.6
110 to 119	2	20.0	6	25.0	22	31.5	12	15.6	8	19.8	4	50.0	54	23.4
120 to 129	1	10.0	6	25.0	21	30.1	19	24.7	9	21.2	2	25.0	58	25.1
130 to 139	...	....	3	12.5	8	11.4	10	13.0	10	23.6	...	....	31	13.4
140 to 149	...	....	1	4.2	1	1.4	8	10.4	3	7.1	1	12.5	14	6.1
150 to 159	...	....	...	....	1	1.4	4	5.2	4	9.4	...	....	9	3.9
160 to 169	...	....	...	....	...	....	3	3.9	...	....	...	....	3	1.3
170 to 179	...	....	...	....	...	....	...	....	...	....	...	....	...	—
180 to 189	...	....	...	....	...	....	1	1.3	...	....	1	12.5	2	0.9
Total	10		24		70		77		42		8		231	
Mean	107.5 ± 2.0		115.1 ± 2.0		115.4 ± 1.0		121.1 ± 1.6		124.2 ± 1.4		125.0 ± 5.4		118.9 ± 0.76	

TABLE V.—DISTRIBUTION OF DIASTOLIC PRESSURE IN PERNICIOUS ANEMIA—FEMALES.

Pressure, mm. Hg.	Up to 29 years.		30 to 39 years.		40 to 49 years.		50 to 59 years.		60 to 69 years.		70 years and over.		All ages.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Up to 49	2	20.0	1	4.2	5	7.2	8	10.4	3	7.1	...	....	19	8.2
50 to 59	4	40.0	6	25.0	12	17.2	13	16.9	9	21.4	2	25.0	46	19.9
60 to 69	3	30.0	10	41.7	23	32.9	27	35.1	18	42.8	2	25.0	83	35.9
70 to 79	...	....	4	16.7	22	31.5	19	24.7	9	21.4	4	50.0	58	25.1
80 to 89	1	10.0	3	12.5	8	11.4	7	9.1	2	4.7	...	....	21	9.1
90 to 99	...	....	...	....	...	....	3	3.9	1	2.4	...	....	4	1.7
100 and over														
Total	10		24		70		77		42		8		231	
Mean	57.7 ± 1.0		65.1 ± 1.0		64.3 ± 0.75		64.8 ± 1.1		63.0 ± 0.83		64.0 ± 1.8		64.0 ± 0.49	

observations is so small as to make the probable error of the mean very large. They are made still more significant when we recall that the life insurance figures are too low, especially for the older age groups.

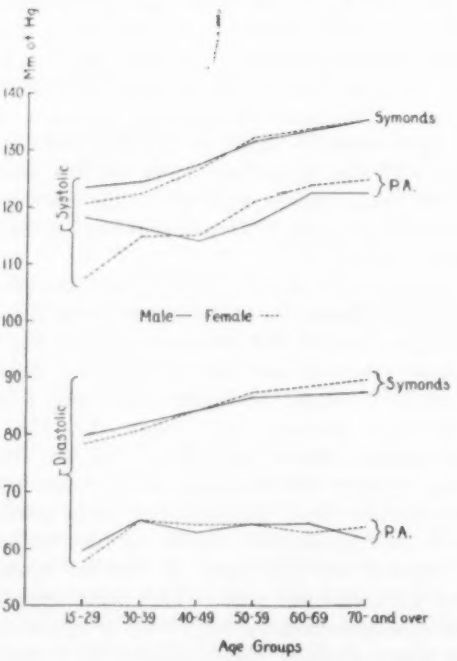

FIG. 1.—Blood-pressure averages of insurance risks (Symonds) and pernicious anemia patients.

On the other hand, if we compare our results with those of Alvarez given in Table I, we note the still greater difference between the

corresponding means. For example, the mean of the systolic pressure of men, as given by Alvarez, is 134.7 ± 0.7. The corresponding mean of our series is 117.9 ± 0.66. The difference here is 16.8 ± 0.96, which is 17.5 times its probable error and is therefore very significant. Our mean, corrected for the age distribution of Alvarez' cases, would be still lower, and the difference larger and more significant.

Hypotension. The study of hypotension and hypertension in pernicious anemia, or, in fact, in any disease, is made difficult by the absence of statistical data as to the frequency of these two conditions in the population at large. The life insurance figures, quite inadequate from the point of view of the study of hypertension, probably serve as a fairly good index of the incidence of hypotension, because, as a rule, the life insurance companies do not reject applicants for hypotension, unless it is extreme. Unfortunately, their data are not arranged in a way that gives us its incidence for the separate age groups, so that a comparison with our results by age is not possible. Therefore, we must compare the results for all the age groups combined.

Dublin, Fiske, and Kopf,[14] in 16,662 males examined at the Life Extension Institute, found that 2.4 per cent had a systolic pressure 25 mm. or more below the average for their age. The lower limits of normal here ranged from 95 to 110 mm. for the different ages. MacKenzie,[15] in a discussion of diastolic pressure, states that in 21,363 males there were 55 cases, or 0.3 per cent, with a diastolic pressure of 35 to 57 mm. Hg. Our study, on the other hand, shows that out of 269 males there were 11.5 per cent with a systolic pressure below 100 mm., and 30.5 per cent with a diastolic pressure below 60 mm.

There are various other figures found in the literature which may throw some light on the incidence of hypotension in normal people. Addis[16] found 8 per cent of 300 soldiers, ages ranging from twenty-one to thirty-one years, under uniform daytime conditions, had a systolic pressure of 100 mm. and lower, and also 8 per cent had a diastolic pressure of 60 mm. and lower. Of 138 normals over nineteen years of age, Stocks and Karn[9] did not find any with a systolic pressure below 102 mm. and only 1 case with a diastolic pressure lower than 60 mm. Friedlander,[4] in reviewing the work of various authors on hypotension, comes to the conclusion that the incidence of hypotension (110 mm. or less for systolic) in young adults is about 2.5 to 3.5 per cent. This percentage is rather high, if we take into consideration the high level of hypotension which he set. We can also calculate the incidence of hypotension in the material studied by Alvarez and by Dunham. These results are compared with our own on pernicious anemia patients in Table VI. The relatively high percentages of low blood pressures in our series is striking, especially the low diastolic pressures. The comparison

is all the more impressive when we correct* our results according to the age distribution of Dunham's material. The corrected percentages for our cases (males) are 17.0 and 47.9 for systolic and diastolic hypotension respectively, as opposed to 3.1 per cent and 1.6 per cent in Dunham's cases.

TABLE VI.—COMPARISON OF PERCENTAGE INCIDENCE OF HYPOTENSION (BELOW 100 MM. SYSTOLIC, OR BELOW 60 MM. DIASTOLIC) IN PERNICIOUS ANEMIA, IN ALVAREZ'S PRIVATE PATIENTS, AND IN DUNHAM'S ARMY OFFICERS.

	Up to 29 years.		30 to 39 years.		40 to 49 years.		50 to 59 years.		60 years and over.		All ages.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Systolic:												
P. A. cases	0.0	10.0	3.8	8.3	17.6	12.9	11.6	13.0	9.2	4.0	11.5	10.4
Alvarez*	1.5	0.3	1.6	1.7	1.8	0.7	2.7	0.0	—	—	1.9	0.8
Dunham†	3.8	....	3.5	....	2.1	....	0.9	....	3.2	....	3.1	
Diastolic:												
P. A. cases	42.8	60.0	19.2	29.2	32.5	24.4	32.8	27.3	27.7	28.0	30.5	28.1
Alvarez	....	2.5	....	0.3	....	0.0	....	0.0	....	—	....	0.7
Dunham	2.7	....	1.6	....	0.7	....	0.6	....	1.6	....	1.6	

* Results for females from combined figures for thin, normal, and stout groups.
† The figures are for cases below 105 mm. systolic.

We think it pertinent and of interest to introduce at this point the findings of various workers regarding the frequency of hypotension in two important pathologic conditions. Joslin,[17] in the study of blood pressure in diabetics, found 35 out of 500, or 7 per cent, with a systolic pressure of 100 mm. or less. This figure is somewhat high compared to our approximate figure of 11 per cent for systolic hypotension. However, if we include in our count those cases with a systolic pressure of 100 mm., we add 4.5 per cent to our result. This fact is explained by the tendency to read in round numbers, and consequently discounts the relatively high result obtained by Joslin.

Much has been written about low blood pressure in pulmonary tuberculosis, particularly by the French workers. However, we have been unable to find an adequate statistical study of this question, and the results of various investigators differ markedly. Naucler,[18] reviewing much of the available data on this subject, emphasized this diversity of opinion. His own results on 84 cases,† excluding all cardiorenal cases and high initial pressure readings, give somewhat lower pressure averages and an incidence of systolic

* This is done by adapting the method used in correcting crude mortality rates—see Pearl, Raymond: Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, Chap. IX.
† Terminal cases not included.

hypotension of 10.7 per cent. De Bloeme[19] found hypotension in 1.4 to 8.3 per cent, depending on the stage of the disease, and an average of 5 per cent in 500 cases of all types. In a recent study of 701 tuberculous patients, Stivelman[20] found the average pressures, both systolic and diastolic, to be normal in early cases and slightly lower than normal in late cases. From the foregoing, it is evident that we have found a higher incidence of hypotension in pernicious anemia than in such a wasting disease as tuberculosis.

TABLE VII.—COMPARISON OF PERCENTAGE INCIDENCE OF HYPERTENSION* IN INSURED RISKS AND IN PERNICIOUS ANEMIA PATIENTS.

	Up to 29		30 to 39		40 to 49		50 to 59		60 and over.		All ages.		
	S.† (%).	P. A. (%).	S.† (%).	P. A. (%).	S.† (%).	P. A. (%).	S.† (%).	P. A. (%).	S.† (%).	P. A. (%).	S.† (%).	P. A. (%).	C.‡ (%).
Systolic:													
Male	1.9	0	3.8	0	9.1	1.5	19.2	10.7	30.7	10.8	5.7	7.0	2.30
Female	0.4	0	2.1	0	9.8	1.4	21.8	14.3	20.6	12.0	3.5	7.8	1.80
Diastolic:													
Male	2.8	0	5.6	0	10.9	0	18.0	1.0	21.9	0	6.9	0.4	0.18
Female	1.1	0	3.2	0	9.6	0	23.1	1.3	20.0	0	4.1	0.4	0.11

* Systolic over 140 mm.; diastolic over 94 mm.
† Symonds.
‡ Corrected.

Hypertension. As stated above, the incidence of arterial hypertension in the general population, irrespective of its origin, is practically unknown. We can only reach an approximation of it from life insurance data and from data based on patients. The one gives us too low a figure; the other too high a figure. Dublin, Fiske and Kopf[14] found 7.5 per cent had a systolic pressure 20 mm. or more above the average for age, their upper limits of normal ranging from 140 to 155 mm. for the different age groups. The significance of this figure is partly lost by their failure to consider diastolic pressures, inasmuch as most clinicians are now agreed that arterial hypertension can be estimated more correctly from the diastolic rather than from the systolic pressure. This deficiency, however, is supplied by MacKenzie[15] who found 7.2 per cent of 21,363 males had a diastolic pressure of 103 to 160 mm. of Hg. inclusive. These results are only slightly higher than those found by Symonds, which we have tabulated in Table VII. The latter were obtained from his tables in which he gives the percentages of cases above 140 mm. systolic and above 94 mm. distolic excluded. Similarly, the incidence of hypertension, as obtained from the data of Dunham[11] (see Fig. 2), is approximately the same as the above-mentioned figures of the insurance companies.

In contrast to these, we have the high figures for the incidence of hypertension in the studies based on patients. Janeway,[21] in

7872 private patients, found 11.1 per cent showed at some time a systolic pressure of 165 mm. or over. This percentage is probably low because a great many readings were taken by palpation. Moreover, the diastolic pressure was not considered at all. In a more

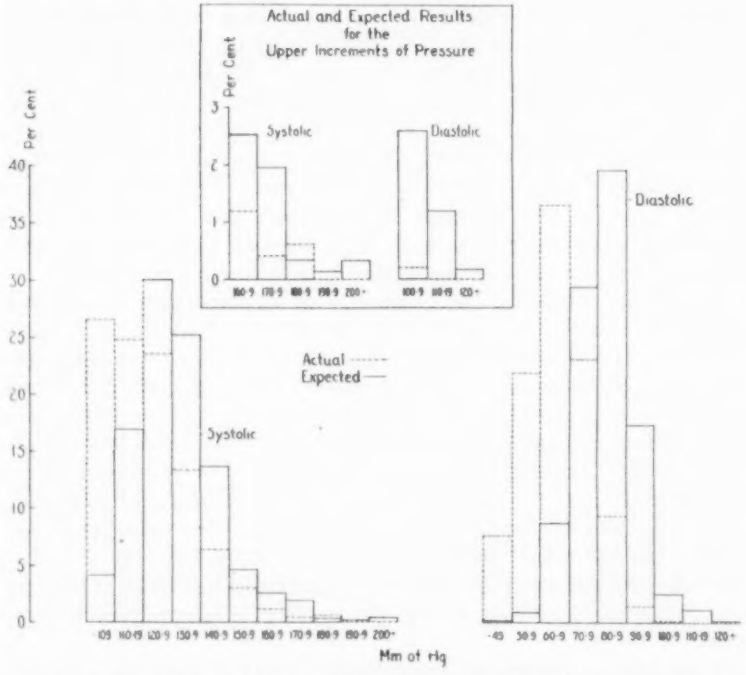

FIG. 2.—Distribution of blood pressure in pernicious anemia actually observed (interrupted line) compared with the expected distribution of blood pressure for normal persons based on Dunham's[11] results.

recent study, also based on private patients, Alvarez[10] found the following incidence of hypertension:

	Male,	Female.	
	systolic (over 159 mm.).	Systolic (over 159 mm.).	Diastolic (over 99 mm.).
16 to 29 years (per cent) . .	3.0	2.7	3.9
30 to 39 years (per cent) . .	3.8	5.8	10.5
40 to 49 years (per cent) . .	9.7	18.7	19.3
Over 50 years (per cent) . .	28.0	41.2	36.0
All ages (per cent)	11.6	15.9	16.9

The diastolic pressure of males was not studied in his papers. These figures are evidently high, especially for diastolic hypertension, in spite of the high normal limits which we set arbitrarily. The reasons for these high values have been stated above in one of the opening paragraphs. The objection to studies based on private patients is avoided by studies on hospital patients. Weitz[22] found

that 8.7 per cent of 359 ambulatory clinic patients, age forty-five years and over, had a systolic pressure over 160 mm. This figure is low for this particular study, because he excluded all patients with complaints relative to the heart or with symptoms pointing to hypertension, and those with nephritis and Addison's disease. A more representative value is given by Cadbury[23] in a study based on the first 3000 admissions to the Peter Bent Brigham Hospital, in whom at least two tests of pressure were taken. He found that 301, or 10 per cent of the cases, had at least one reading of 160 mm. or more. Dividing this group of cases with systolic hypertension according to their diastolic pressures, he found that 272 cases or 9.1 per cent had, in addition, a diastolic pressure over 90 mm. The latter represent mainly cases of true arterial hypertension, but not all of them. There are a few such cases with high diastolic pressures, but with relatively low systolic pressures due to a failing myocardium.

Let us now consider the frequency of hypertension in our own cases. In Table VII our results for systolic hypertension (over 140 mm.) and diastolic hypertension (over 94 mm.) are compared with those of Symonds. Up to the age of fifty years, the differences in systolic hypertension are marked; after this age, however, it is fairly common in pernicious anemia patients, but much less than in the controls. For the whole series the percentages (corrected for the age distribution of the controls) are 2.3 for males and 1.8 for females, against 5.7 and 3.5 for the males and females of the controls respectively. In the whole series of 500 cases, there are only 2 with a diastolic pressure exceeding 94 mm., a corrected incidence of 0.15 per cent, while the incidence among the controls is approximately 6 per cent.

If we look at the results from another point of view, the expected incidence of hypertension in our cases, if they were as normal as Symonds', is as follows: Systolic hypertension—male, 17.5 per cent; female, 14.9 per cent; diastolic hypertension—male, 15.6 per cent; female, 15.3 per cent. These results are evidently much higher than the actual results obtained. Again, in Fig. 2, the 'spread' of blood pressure in all our cases, as actually found, is compared with that expected for our cases, assuming that Dunham's results for the different age groups are normal. From the graph it is obvious that hypertension is much less frequent in our cases than would be expected if they were normal. For example, we find 1.6 per cent of the cases with a diastolic pressure 90 mm. and over, whereas we expect 21.2 per cent in a corresponding normal group.

The study of Cadbury[23] seems to satisfy most of the requirements for a control to our series in the study of hypertension. Analyzing our cases on a basis similar to his, we find that 22 or 4.4 per cent had at least one systolic-pressure reading of 160 mm. or over. Eleven of these, however, had average pressures below 160 mm. and only 1 had a diastolic pressure exceeding 90 mm. This is the only

case which can be called definitely arterial hypertension. There are 2 other cases with a diastolic pressure over 90 mm.: one had an initial pressure reading of 130 systolic and 100 diastolic, but no subsequent measurements; the other had an initial reading of 158 systolic and 102 diastolic, and a subsequent reading of 155 systolic and 84 diastolic. If we include these 2 cases, the maximum incidence of hypertension is 0.6 per cent, but the probability is that the true figure is closer to 0.2 per cent. In any event, our results agree fairly closely with those of Giffin and Bowler[6] (0.64 per cent).

We can also consider the incidence of hypertension from another point of view, namely, as a function of age. On this basis, we can call hypertension any systolic pressure exceeding the average for age* by 15 mm., and any diastolic pressure exceeding the average for age* by 10 mm. Analyzed in this way, our cases yield 24 with systolic hypertension and only 1 with diastolic hypertension. This is the case referred to above with a blood pressure of 130 systolic and 100 diastolic. There are no cases with both systolic and diastolic hypertension, a very significant finding.

It would be of interest to compare the incidence of hypertension in other diseases with that in pernicious anemia, but in tuberculosis alone can we find adequate data. It is agreed by most writers in this field that the late cases of tuberculosis are often associated with some lowering of blood pressure. Nevertheless, De Bloeme[19] found that 11.2 per cent of his tuberculous patients had a systolic pressure of 140 mm. and over, the stage of the disease having little influence on this figure. Stivelman,[20] also, found that 10 per cent of his patients had a systolic pressure above 135 mm. for the ages sixteen to thirty years, and above 140 mm. for the ages over thirty years. These results correspond closely with the available figures for normal people. Consequently, it seems that the presence of hypotension in tuberculous patients has very little effect on the incidence of hypertension, whereas in a series of pernicious anemia patients it is associated with an almost complete disappearance of hypertension.

Pulse Pressure. It has already been indicated that the pulse pressure in pernicious anemia is high, and this is made the more evident from Table VIII and Fig. 3., where it is compared with the pulse pressure of insured risks.[24] We see that the pulse-pressure averages in pernicious anemia are higher than the corresponding normal averages by 9 to 17 mm. of Hg., this finding being at variance with that of Wilson and Evans[8] who state that the pulse pressures in their pernicious anemia cases showed nothing characteristic. The probable errors of these differences are sufficiently small so that great significance can be attached to the latter. The low diastolic pressure and the high pulse pressure seem to be a compensatory mechanism on the part of the body to maintain the required gaseous exchange.

* The averages given by Symonds are used.

Theoretically, a diminished hemoglobin content of the blood must lead to a speeding up of the circulation. Plesch[25] has demonstrated that actually the minute volume in pernicious anemia and in other anemias is increased. Blumgart[26] also finds the minute volume increased in the neighborhood of 40 per cent for a group of anemias

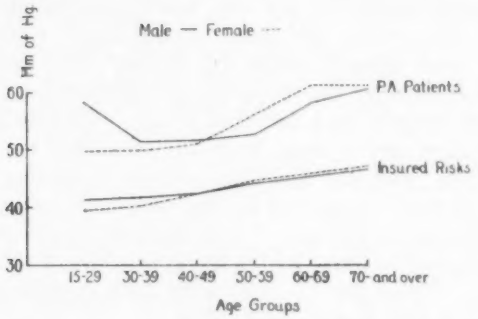

FIG. 3.—Pulse-pressure averages of insured risks[24] and of pernicious anemia patients.

of various sorts, including pernicious anemia. Normally this can be brought about either by a speeding up of the heart rate or by a diminution in the peripheral resistance, or by both. Since Cabot[1] has shown that there is no marked change from the normal in the heart rate of pernicious anemia patients, we must assume that the reduction in peripheral resistance is the chief factor here. The

TABLE VIII.—THE PULSE PRESSURE OF INSURED RISKS AND OF 500 PERNICIOUS ANEMIA PATIENTS.

	Male.			Female.		
	Insured risks.*	Pernicious anemia.	Difference.	Insured risks.*	Pernicious anemia.	Difference.
Up to 29	41.3	58.7	17.4	39.4	49.8	10.4
30 to 39	41.7	51.4	9.7	40.2	50.0	9.8
40 to 49	42.4	51.7	9.3	42.4	51.1	8.7
50 to 59	44.4	52.9	8.5	44.7	56.3	11.6
60 to 69	46.9	58.3	11.4	47.5	61.2	13.7
70 and over		60.8	13.9		61.0	13.5
All ages	42.1	54.0	11.9	40.8	54.9	14.1

* The age groups are lower by two years than groups indicated.

consequence of this lowering of diastolic pressure is a more rapid filling of the veins and of the heart, so that the heart has more blood to pump. According to Starling's Law of the Heart, the heart responds to an increased filling of its chambers by putting out more blood per beat. This, of itself, brings about an increased pulse

pressure, as has been shown by Read,[27] studying the pulse pressure in heart block, and by Lawrence, Hurxthal and Bock,[28] studying the changes in circulation due to posture, and by Plesch[25] who has shown that increase in volume flow is due chiefly to large pulse volume.

The situation here is analogous to that seen in aortic regurgitation. In the latter the increased filling of the ventricle is due to the backflow from the aorta through the incompetent aortic valves; while in the former, the increased filling is due to the more rapid emptying of the arterial system into the venous and thence into the heart. The result is the same in both—a low diastolic and a high pulse pressure. Such a state, if long maintained, may lead to cardiac hypertrophy. Actually this theoretical concept is confirmed by Cabot,[29] who found cardiac hypertrophy and dilatation in 22 out of 23 pernicious anemia patients coming to autopsy.

Blood Pressure and Recovery. Giffin and Bowler[6] come to the conclusion that hypotension in pernicious anemia may be due to some other factor than anemia, inasmuch as the blood pressure, in their experience, rarely returns to normal with an elevation of the blood count. On the other hand, Minot and Murphy[3] state that the blood pressure usually attains a normal level as improvement in the blood takes place on the liver diet. Our own knowledge of this subject is limited to 44 cases which improved on the liver diet and had blood-pressure readings during the course of improvement. The average of the initial readings, before improvement began, was 122.5 for systolic and 63.8 for diastolic pressure; the average of the final readings recorded was 118.3 and 66.3 for systolic and diastolic respectively. Owing to the fact that the probable error of these results is about 1.2, conclusions based on them must be drawn with extreme care. About an equal number of cases show a fall as show a rise in pressure. However, we can say definitely that, as improvement takes place, there is a tendency for the systolic pressure to fall and for the diastolic to rise, so that the pulse pressure is appreciably lowered.

Summary and Conclusions. 1. Analysis of the blood pressure in 500 cases of pernicious anemia shows only slight variation in the averages due to age or sex. Compared, however, with average figures for normal people, it is significantly lower.

2. The incidence of systolic hypotension in the series used as controls varies from 2 to 3 per cent, and of diastolic from 0.3 to 1.6 per cent. The incidence in our series of pernicious anemia patients is about 11 per cent for systolic and about 30 per cent for diastolic hypotension. These percentages, corrected for the age distributions of the controls, are still higher. Hypotension is a more frequent condition in pernicious anemia than in tuberculosis.

3. The incidence of hypertension in the accepted risks of life insurance companies is somewhat lower than in miscellaneous

material or private patients . . . . . 5 to 7 per cent and 10 to 15 per cent respectively. Its incidence in the general population must lie in between these percentages. On the other hand, in our pernicious anemia series we find systolic hypertension in about 2 per cent and diastolic in about 0.15 per cent of the cases. Analyzing our cases from both points of view, we find only 1 case definitely of arterial hypertension and 2 more which may possibly be that.

4. It appears that in pernicious anemia hypotension is associated with an almost complete disappearance of hypertension, whereas in tuberculous patients, the existence of hypotension has little effect on the frequency of hypertension. The infrequency of hypertension in pernicious anemia impresses us as of distinct interest, being practically as rare as is the presence of free hydrochloric acid in the gastric juice. But, of course, until further control data on other anemias has been secured, no diagnostic weight can be laid on blood pressure.

5. The pulse pressures in pernicious anemia are higher than the corresponding normal ones by 9 to 17 mm. of Hg. This increased pulse pressure is apparently a feature of an increased volume flow of blood of a compensatory nature, and finally results in hypertrophy of the cardiac musculature.

6. With improvement in blood picture the pulse pressure tends to diminish.

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POLLEN ALLERGY.*

Skin Reactions of Patient Before and After Treatment with Spring (Grass) Pollens.

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In a previous communication, one of us[1] emphasized the factors which must govern one in the treatment of a case of pollen allergy. Briefly these are concerned with the correlation of the distribution, dates of pollination and relative abundance of the pollens to which the patient reacts with the domicile and calendar period of symptoms. A method of treatment was outlined setting an optimal dosage of pollen antigen. This, as every other writer on the treatment of pollen allergy has done, was set empirically. The present study was undertaken with a view to eliminate such empiricism and to establish an objective criterion of the adequacy of treatment.

Two methods of determining skin reactivity are available, the

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scratch[2, 3] test and the intradermal test.[4, 5] It is not the purpose of this paper to enter into a discussion of the relative merits[4] of these two tests. Most workers agree that the latter method is the more sensitive, and that a negative reaction by this method is more apt to indicate a lack of skin sensitivity than would a similar reaction when obtained by the scratch test. Although the skin tests are used to detect sensitivity, there seems to be a paucity of available data as to the effect of any course of treatment upon the skin reactions. The early workers[6, 7, 8, 9] express their belief, though no data are supplied, that the skin reaction (scratch) is a reliable guide to treatment. More recently, Kolmer[10] stated, although here again no data[11] are offered, that the specific treatment of hay fever and bronchial asthma by subcutaneous injection of extracts of the exciting agent or agents is a process of true desensitization by which anaphylactic antibody in the sensitized cell is exhausted. Phillips[12] is quite emphatic in insisting that skin desensitization must be obtained no matter how many doses are required nor how large. Another group of workers, especially Cooke[13, 14] and his associates, are of the opinion that treatment of the allergic patient has little or no effect upon the skin sensitivity. In later articles[15,16] they modify somewhat their previous statements, and apparently feel that skin reactivity may be decreased though not regularly, and in either case do not attach much importance to it. A somewhat similar or mid position is taken by Caulfield,[17] Larsen[18] and Rackemann.[19]

Methods. *I. Testing.* It is the custom in this Clinic to retest our patients to spring (grass) pollens in November or December, unless they are new patients that have been tested for the first time within two or three months, in which case the original test may not be repeated. The antigen is prescribed after due consideration of the facts mentioned in the introduction and the treatments are given in most cases before the onset of the grass-pollen season, usually at weekly intervals, so that the last treatment of the course shall be given about a week or two before pollination begins. We are most emphatically not in accord with the school who believe that a single pollen is satisfactory for the treatment of multiple grass-pollen sensitizations. Three and occasionally six pollens are included in the treatments, and a minimum of fifteen injections are given.

II. Pollen Solutions. The standard extracting and diluting fluids are made as follows:[20]

Phosphate Buffer Solutions.

0.3 M sodium dihydrogen phosphate.
41.4 gm. $NaH_2PO_4.H_2O$ per liter.
0.3 M disodium hydrogen phosphate.
107.5 gm. $Na_2HPO_4.12H_2O$ per liter.

Standard Glycerol Extracting Fluid.

1 volume 0.3 M sodium dihydrogen phosphate.
4 volumes 0.3 M disodium hydrogen phosphate.
5 volumes c.p. glycerol.

Standard Alcohol Diluting Fluid.

1 volume 0.3 M sodium dihydrogen phosphate.
4 volumes 0.3 M disodium hydrogen phosphate.
5 volumes 30 volume per cent ethanol.

Standard Phenolic Extracing Fluid.

1 volume 0.3 M sodium dihydrogen phosphate.
4 volumes 0.3 M disodium hydrogen phosphate.
5 volumes 1.0 per cent phenol solution or 0.6 per cent tricresol.

The above described fluids when made will have an hydrogen-ion concentration represented by pH 7.4 and are isotonic in total salt content. They are strongly buffered at pH 7.4 and small amounts of acid or alkali will not appreciably change the hydrogen-ion concentration.

Stock Pollen Extracts. 2 gm. of desiccated pollen are extracted with occasional shaking for twenty-four hours or longer, with 100 cc. of standard glycerol extracting fluid. The resultant extract is sterilized and clarified by filtration through a sterile Berkefeld filter. The final pollen extract so obtained is 1 to 50 and contains 20,000 pollen units per cubic centimeter. (The pollen unit used here is defined as the active pollen substance extractable from 10^{-6} gm. pollen, first defined by Noon for Timothy pollen.)

Solutions for Skin Tests:

(*a*) *Cutaneous Test Dilution* (*for Scratch Tests*): 1 to 50, which is the stock extract. This is applied on flexor surface of forearm of adults or on the back if the patient is a child.

(*b*) *Intracutaneous Test Dilution* (*for Intracutaneous Tests*): 1 to 1000, which is obtained by diluting 0.5 cc. of the stock extract with 9.5 cc. of standard alcohol diluting fluid. The area used for this test is the lateral aspect of the upper arm.

The antigens are prepared as follows:

Standard Dilutions (Three Antigens).

1 to 50, which is made from 1 cc. each of three pollen stock extracts.

1 to 500, which is obtained by diluting 0.3 cc. of the 1 to 50 dilution with 2.7 cc. of standard alcohol diluting fluid.

1 to 5000, which is obtained by diluting 0.3 cc. of the 1 to 500 dilution with 2.7 cc. of standard alcohol diluting fluid.

III. Treatments. It is customary to use these three dilutions although a few of the more sensitive patients start with dilutions of 1 to 50,000. In any event, the first dose consists of 0.1 cc. of the most dilute solution; this is increased by tenths to 0.5 cc. and the sixth injection begins again at 0.1 cc. of the next concentration, and so on until all dilutions have been used. About two-thirds of the patients are treated with an antigen containing three pollens. Nearly half as many receive six pollens; that is, two sets of three pollens each, given at the same time, thus doubling the volume mentioned above, and a few patients are treated to but one pollen. When the lowest concentration is 1 to 5000 a minimum of fifteen treatments is given and the use of 1 to 50,000 adds five more to this minimum. A study[21] of the pollen frequency in the antigens indicates that Cynodon dactylon (Bermuda), Lolium perenne (Ray) and Poa praetensis (Kentucky blue grass) are the pollens most commonly prescribed in this Clinic. The first mentioned is used in a ratio of about 2 to 1 of either of the other two pollens. More complete data[22] regarding each pollen in the antigen of all patients included in this report will be published elsewhere.

No attempt has been made in this study to correlate the clinical condition of the patient with skin reactions.[6] Numerous reports from the clinics of Piness, Cooke and Walker demonstrate the efficacy of pollen therapy and the clinical results justify the procedure. The final and most important clinical test can only be answered at the end of the pollen season when it is determined whether the patient had less hay fever than when untreated.

TABLE I.—PATIENTS TREATED WITH CYNODON DACTYLON (BERMUDA GRASS).

Patient No.	Sex.	Age.	Previous treatments with Bermuda grass.	No. of treatments this course.	Skin reactions.			Remarks.
					Before treatment.	2 weeks after treatment.	4 weeks after treatment.	
79	M.	16	16	20	iv	—	?	
9	M.	56	none	15	iv	4	?	
45	M.	45	55	23	iv	4	4	
63	F.	30	118	15	iv	4	4	
64	F.	31	none	16	iv	4	4	
2	M.	9	50	15	iii	?	2	
14	F.	5	none	16	iii	neg.	neg.	
26	M.	8	none	16	iii	—	?	
27	F.	11	none	20	iii	2	—	
50	F.	39	15	20	iii	—	3	
48	F.	11	72	24	iii	4	4	
12	M.	52	36	22	4	—	?	
28	M.	38	21	15	4	—	4	
31	F.	40	26	17	4	3	?	
37	M.	44	none	15	4	?	—	
38	F.	39	27	15	4	3	4	
66	F.	30	21	20	4	3	?	
67	M.	41	12	18	4	—	?	
71	F.	45	21	23	4	4	2	
62	M.	24	none	21	4	4	?	
10	F.	41	45	15	3	—	?	
32	M.	11	29	15	3	2	2	
44	F.	47	33	15	3	—	2	
54	F.	30	none	16	3	—	—	
55	F.	27	none	17	3	?	—	
76	M.	31	13	16	3	2	—	
74	F.	14	41	21	3	4	—	
3	M.	18	?	15	ii	4	4	
5	F.	59	17	15	2	—	—	
24	M.	62	16	15	2	—	—	
57	M.	29	53	16	2	?	3	Formerly 4 plus
40	M.	36	15	16	—	—	—	Formerly 4 plus
42	F.	39	23	15	—	—	—	Formerly 3 plus
49	M.	10	45	17	neg.	—	—	Formerly iv plus
52	M.	12	76	15	neg.	—	—	Formerly iv plus
59	F.	8	15	15	neg.	—	—	Formerly positive by scratch
8	F.	48	none	16	—	4	2	
13	M.	36	26	21	neg.	2	?	Formerly 4 plus
17	F.	24	35	15	—	3	—	Formerly 4 plus
36	M.	11	18	15	neg.	3	4	Formerly iv plus
39	M.	38	none	15	—	4	—	
43	M.	48	46	15	—	—	3	Formerly 4 plus
60	M.	24	17	15	neg.	4	3	Never positive by scratch
77	M.	21	40	15	neg.	—	4	Formerly iv plus
78	M.	46	95	20	neg.	4	?	
6	F.	45	10	24	?	4	2	
22	M.	26	22	20	?	4	4	Formerly 4 plus
23	M.	33	19	20	?	?	4	Formerly 4 plus
33	F.	31	11	15	?	4	?	Formerly iv plus
34	F.	54	9	15	?	—	?	Formerly 2 plus
58	M.	45	19	17	?	—	—	Formerly iii plus
80	F.	30	17	19	?	—	?	Formerly 4 plus
81	M.	21	13	20	?	—	4	Formerly 4 plus

Explanation of Tables. The diagnoses in these cases are hay fever or asthma, or both, those with the two conditions predominating.

In all tables the same schema have been followed. When a patient-number appears in more than one table it represents the same individual, and thus one may observe that several of these patients received two or more of the pollens discussed below.

TABLE II.—PATIENTS TREATED WITH LOLIUM PERENNE (RAY GRASS).

Patient No.	Sex.	Age.	Previous treatments with Ray grass.	No. of treatments this course.	Skin reactions.			Remarks.
					Before treatment.	2 weeks after treatment.	4 weeks after treatment.	
23	M.	33	none	20	iv	?	—	
45	M.	45	15	23	iv	4	3	
58	M.	45	none	17	iv	—	—	
81	M.	21	none	20	iv	2	4	
22	M.	26	22	20	iv	4	4	
48	F.	41	16	24	iv	4	4	
49	M.	10	30	17	iii	—	—	
63	F.	30	86	15	iii	4	3	
1	F.	23	none	20	4	—	?	
4	F.	33	23	15	4	3	—	
28	M.	38	21	15	4	—	2	
31	F.	40	33	17	4	2	?	
39	M.	38	none	15	4	—	2	
55	F.	27	48	17	4	?	3	
61	F.	65	none	21	4	2	?	
73	M.	15	none	16	4	—	3	
43	M.	48	31	15	4	4	4	
32	M.	11	none	15	3	2	3	
37	M.	44	none	15	3	?	—	
75	M.	34	none	15	3	—	—	
71	F.	45	21	23	ii	4	2	
11	F.	13	32	15	neg.	2	?	Formerly iii plus
12	M.	52	16	22	...	4	?	Formerly 4 plus
13	M.	36	26	21	neg.	4	?	Formerly 4 plus
20	F.	53	none	17	...	4	?	Never positive
78	M.	46	30	20	neg.	4	?	Formerly iv plus

Reactions. When indicated by roman numerals or the word "neg" it signifies that the results were obtained by the use of the scratch test; those obtained by the intradermal test are designated by arabic numerals or a (−) as the case may be. Where tests were not made, the interrogation mark (?) is used. It was intended that tests should be made two and four weeks after the last treatment, but in many instances the patients failed to return for one or the other test. These results were obtained in April and May 1927 and all tests made with same lot of test solutions.

Degree of Reaction. The cases are grouped in approximately descending order of skin sensitivity to the scratch and intradermal

tests respectively. In many cases patients are negative by the scratch test and a 4+ by the intradermal method, in such a case the difference in concentration of pollen extract in test solutions is of interest. Therefore, a iv+ before and a 4+ after treatment may actually represent a decrease in skin sensitivity but will not be so considered in this study. A 2+ (intradermal) is merely a questionable reaction and is classed as a (−) intradermal. A 3+ reaction by either test has the following significance; a larger wheal than the control, one or two small pseudopods and is usually surrounded by an area of erythema. The 4+ in either case refers to the strongly positive reaction, with definite pseudopods and the wheal is usually more than 1.5 cm. in diameter.

TABLE III.—PATIENTS TREATED WITH POA PRÆTENSIS (KENTUCKY BLUE GRASS).

Patient No.	Sex.	Age.	Previous treatments with this pollen.	No. of treatments this course.	Skin reactions.			Remarks.
					Before treatment.	2 weeks after treatment.	4 weeks after treatment.	
3	M.	18	?	15	iv	—	4	
22	M.	26	none	20	iv	—	4	
27	F.	11	none	20	iv	—	—	
36	M.	11	none	15	iv	4	3	
48	F.	41	39	24	iv	3	3	
49	M.	10	35	17	iv	—	—	
78	M.	46	40	20	iv	2	?	
79	M.	16	none	20	iv	—	?	
45	M.	45	15	23	iv	4	4	
77	M.	21	22	15	iv	4	?	
15	M.	54	none	16	4	—	—	
28	M.	38	21	15	4	2	—	
38	F.	39	none	15	4	—	3	
46	F.	45	none	16	4	—	—	
69	M.	33	76	15	4	2	—	
72	F.	21	none	15	4	2	2	
76	M.	31	13	16	4	—	2	
43	M.	48	31	15	4	4	4	
55	F.	27	48	17	4	?	4	
61	F.	65	none	21	4	4	?	
53	M.	11	none	15	3	?	—	
66	F.	30	21	20	3	2	?	
26	M.	8	none	16	neg.	—	?	Never positive
52	M.	12	53	15	neg.	—	—	Formerly iv plus
13	M.	36	26	21	neg.	4	?	Formerly 4 plus
41	M.	45	15	16	neg.	4	4	Formerly iv plus
71	F.	45	21	23	neg.	2	—	Formerly 4 plus
23	M.	33	19	20	?	?	—	

Nineteen of the first 27 patients in this table, those with a definite positive reaction, obtained some decrease in their reaction as a result of treatment. It is of interest to note that the most sensitive

do not show the greatest decrease in reaction. The last part of the table is of interest in that it shows a tendency to lessened sensitivity as a result of prolonged treatment. Note especially cases 57, 40, 42, 49, 52, 59, 36, 43, 77.

TABLE IV.—PATIENTS TREATED WITH PHALARIS MINOR (SMALL CANARY GRASS).

Patient No.	Sex.	Age.	Previous treatments with this pollen	No. of treatments this course.	Skin reactions.			Remarks.
					Before treatment.	2 weeks after treatment.	4 weeks after treatment.	
3	M.	18	?	15	iv	3	4	
6	F.	45	none	22	iv	2	3	
23	M.	33	none	20	iv	?	—	
26	M.	8	none	16	iv	—	?	
48	F.	41	18	24	iv	4	3	
18	F.	30	none	15	iv	4	4	
22	M.	26	none	20	iv	4	4	
35	M.	28	none	26	iv	4	4	
78	M.	46	20	20	iv	4	?	
79	M.	16	none	20	iii	—	?	
41	M.	45	none	16	iii	4	4	
17	F.	24	none	15	4	3	3	
30	F.	27	none	21	4	—	—	
32	M.	11	none	15	4	—	—	
46	F.	45	none	16	4	2	2	
57	M.	29	none	16	4	?	2	
74	F.	14	none	21	3	—	?	
38	F.	39	none	15	3	2	4	
5	F.	59	15	15	2	—	—	
21	F.	6	none	16	2	—	—	
25	F.	56	16	15	2	—	?	Formerly 3 plus
55	F.	27	33	17	2	?	4	Formerly 4 plus
24	M.	62	16	15	—	—	—	Formerly 4 plus
13	M.	36	none	21	neg.	4	?	Formerly 3 plus
71	F.	45	none	23	—	4	2	

At least 17 of the 26 patients above, showed a diminution in the intensity of the skin reaction following the course of treatments. Numbers 23, 58, 49, 1, 28, 39, 73 and 75 are especially interesting in this connection.

At least 17 of the above 28 patients showed a diminution in the intensity of their skin reaction after treatments. Note especially Nos. 27, 49, 15, 46, 68, 72, 76.

Eleven of the above 25 patients showed a diminution in skin reaction as a result of treatment, especially Nos. 6, 23, 26, 30, 32 and 46. In this case the most sensitive patients did not manifest the greatest reduction.

Discussion of Tables. The age, sex or previous treatment has little evident effect upon the results. In general, we find little

support for the theory that the more sensitive the individual the greater the decrease in skin reaction as a result of treatment. At least 50 per cent of the patients manifested a lessened reaction at the end of the two- or four-week period or both, and this seems to be quite significant when one appreciates that the selection of fifteen as the optimum number of treatments is quite empirical and might easily not apply to every case. The question of whether this decrease of skin reactive capacity should be designated desensitization[10] or hyposensitization[15] is an academic one and is left unanswered. Without committing ourselves to either view we wish to use the former term. Of the cases cited that had a definitely positive reaction before treatments and who were retested at both two and four weeks, the lessened reaction persisted to the fourth week as follows: Tables I and II, 6 patients each; Table III, 9 patients; Table IV, 4 patients. In each table, one may observe that, in the group having a negative reaction before treatments, practically all have previously been strongly positive to the particular pollen and that most of these have had previous treatment with it. This suggests that if treatment is persisted in "skin desensitization" at least between pollen seasons may be more or less permanent.

Conclusions. 1. Comparative data are presented, showing the skin reactions to pollen extracts on patients with asthma and hay fever, prior to and also two and four weeks after completing the usual course of pollen injections.

2. Under the conditions outlined, there has occurred a definite diminution in skin reactivity. In numerous cases, this has persisted at least four weeks after the last treatment, and it appears that prolonged treatment may extend the period to many months—especially between pollen seasons. Perennial treatment may prove to be the best method of maintaining this condition.

3. The factors preventing such "desensitization" seem to be unrelated to age, sex, diagnosis, or previous treatments, but are probably related to individual differences or to the amount of treatment received.

4. As a guide to treatment, it is suggested that each patient be considered as an individual problem, that a minimum number of treatments, fifteen, for example, be given, after which the results of skin tests may be used to determine whether more are needed.

5. Since pollens are included in an antigen or excluded from it on the basis of skin reactions—and this in last analysis is our measure of systemic sensitization or nonsensitization—an attempt at "skin desensitization" seems logical and less empirical than present methods.

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POLLEN ALLERGY. IV.

With Special Reference to Skin Reactions Before and After Treatment With Fall Pollens.

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In the previous report[1] we discussed the current theories regarding the effect of treatment with grass pollens upon the skin reactions to these pollens. Data were presented which showed that the usual course of treatment resulted in a decrease in the reactive capacity of the patient's skin to these pollens in a majority of cases. Whether this should be called desensitization or hyposensitization was not

discussed, but we employed the former term for convenience. We were not prepared then, nor are we now, to make a strict comparison between the skin test and the patient's clinical condition, so the findings were emphasized only insofar as they applied to skin reactions.

It has been suggested that even if it were possible to bring about skin desensitization to grass pollens it would be much more difficult, or impossible to desensitize the skin to ragweed or other fall pollens. No reason was indicated for this assumed difference and it did not appear logical. In order to test this assumption and to furnish further information regarding other factors in skin reactions we have compiled the observations reported herein concerning fall pollens.

Explanation of Methods.—The technique employed in making the pollen extracts and test solutions, the method of performing the intracutaneous test and reading the results have been described.[1] Further description seems unnecessary at this time as the methods employed were identical with those in the previous study. A ++ result is again assumed to actually represent a negative reaction for reasons previously stated. The difficulty encountered in correlating results of scratch and intracutaneous tests has been discussed. A negative scratch test may be a ++++ by intracutaneous; therefore a ++++ (scratch) before treatment and a ++++ intracutaneous after treatment may actually represent a decrease in skin reaction but we will not so consider it. A +++ intracutaneous after treatment in such a case will, however, be considered evidence of skin desensitization.

Sixty-four cases are represented in this study. The patients have been grouped alphabetically and numbered from 1 to 64. Space does not permit publication of the entire table but certain cases have been selected to represent the several phases discussed.

It is of interest in passing to point out the frequency with which certain allergic conditions occur singly or combined in this series. Asthma and hay fever occur together in 25 cases of the 64. Hay fever alone in 16 and asthma alone in but 4 patients. Since asthma is one of the diagnoses in 46 of the 64 cases it is surprising that it occurs alone but four times. Diagnoses were made of asthma, hay fever and eczema in the same individual in 6 instances. The other combinations of diagnoses do not occur in more than 4 patients and will not be discussed. The age or sex of the patient exert no demonstrable influence upon the results, which will be considered below.

The pollens most frequently employed in treatment of fall pollen sensitization belong to one of the following genera:

Ambrosia (Ragweed), Artemisia (Sagebrush), Atriplex (Scales) and Cynodon dactylon (Bermuda grass). Other genera are represented, but not a sufficient number of times to justify consideration of each separately.

SKIN TESTS BEFORE AND AFTER TREATMENT WITH FALL POLLEN.

Patient No.	Sex.	Age.	Diagnoses.	Pollen in antigen.	Pollen tested but not in antigen.	Previous treatments.	No. of treatments this course.	Duration of treatments in weeks.	Skin reactions.			Previous skin reactions.	Remarks.
									Before treatment.	2 weeks after treatment.	4 weeks after treatment.		
3	F	38	HF	Ar (3)	....	None	15	15	iv	–	–		
				At (1)	....	15	..	..	iv	–	–	..	Second test 6 weeks
				C	....	90	..	..	neg	2	2	iv	after last treatment.
					Ar (2)	None	..	..	iii	–	3		
					At (2)	None	..	..	iv	–	–		
					C (1)	None	..	..	iv	–	3		
8	M	42	A	A (1)	....	28	15	15	4	–	–		
			HF	Ar (7)	....	28	..	..	4	–	–		
				At (3)	....	None	..	..	4	–	–		
				C	....	34	..	..	3	–	–		
				F	....	16	..	..	4	–	–		
				X	....	None	..	..	4	–	–		
					Ar (6)	None	..	..	4	2	2		
					At	None	..	..	3	–	–		
9*	M	34	A	Am (1)	....	None	15	14	neg	–	–	4	
			HF	Ar (1)	....	15	..	..	4	–	3		
				Ar (7)	....	None	..	..	3	3	3	4	
				At (5)	....	None	..	..	4	–	–		
				C	....	30	..	..	4	–	4		
				F	....	15	..	..	3	4	3		
					At (1)	15	..	..	3	–	–	3	
10*	F	45	HF	Ar (1)	....	None	15	13	4	4	4		
				Ar (7)	....	None	..	..	4	4	3		
				At (1)	....	None	..	..	4	3	3		
				C	....	33	..	..	3	–	–	4	
				F	....	11	..	..	4	3	4		
				S (1)	....	None	..	..	4	2	3		
					Ar (2)	None	..	..	4	3	3		
12*	M	49	A	A (1)	....	None	15	8	3	–	–		
			HF	At (1)	....	None	..	..	3	–	–		
				C	....	None	23	8	iv	4	4		
				C (3)	....	None	15	8	3	–	4		
					Ar (3)	None	..	..	3	–	–		
					At (6)	None	..	..	3	3	3		
15*	F	53	A	A (1)	....	31	15	14	neg	–	–	iv	
			HF	Ar (7)	....	31	..	..	iii	3	4	iv	
				C	....	61	..	..	neg	–	4	iv	
					A (3)	None	..	..	iv	–	2		
					Ar (6)	None	..	..	iv	4	4		
					At (2)	None	..	..	iii	3	3		
16	F	45	A	Ar (2)	....	15	15	14	4	–	–	4	
			HF	At (3)	....	None	..	..	3	–	–		
			E	C	....	30	..	..	–	–	–	4	
					A (1)	None	..	..	2	–	–	2	
					Ar (1)	None	..	..	2	–	–	2	
					At	None	..	..	–	–	–	–	
17	M	10	A	A (1)	....	None	15	15	3	–	–		
				Ar (2)	....	None	..	..	4	–	–		
				At (6)	....	None	..	..	3	–	–		
					A	None	..	..	3	–	–		
					At (3)	None	..	..	3	–	–		
18	F	37	A	A (1)	....	32	15	16	–	–	–	neg	
			HF	Ar (3)	....	49	..	..	–	–	–	iii	
				At	....	32	..	..	–	–	–	iii	
					A (3)	None	..	..	4	–	–	iv	
					At (1)	None	..	..	3	–	–		
					F	None	..	..	4	–	–		
21*	M	25	A	A (1)	....	None	15	14	iv	4	4		
			HF	Ar (1)	....	15	..	..	neg	4	4	iv	
				Ar (7)	....	15	..	..	iii	4	4		
				At (3)	....	None	..	..	iv	–	–		
				F (2)	....	None	..	..	iv	4	4		
					A	15	..	..	iv	4	4		
22*	F	64	HF	A (1)	....	None	24	14	4	4	4		
			E	Ar (1)	....	28	..	..	4	3	3		
				Ar (2)	....	28	..	..	4	–	–		
				Ar (7)	....	28	..	..	4	–	–		
				At	....	28	..	..	?	–	–	4	
				F (2)	....	None	..	..	4	4	4		
					X (1)	..	..	..	iv	3	4		

SKIN TESTS BEFORE AND AFTER TREATMENT WITH FALL POLLEN.
(*Continued.*)

Patient No.	Sex.	Age.	Diagnoses.	Pollen in antigen.	Pollen tested but not in antigen.	Previous treatments.	No. of treatments this course.	Duration of treatments in weeks.	Skin reactions.			Previous skin reactions.	Remarks.
									Before treatment.	2 weeks after treatment.	4 weeks after treatment.		
24	F	25	A	Ar (1)	....	15	15	12	4	3	2		
			HF	Ar (6)	....	None	..	..	4	–	3		
				Ar (7)	....	15	..	..	4	2	–		
				At (1)	....	None	..	..	4	–	–		
				F	....	15	..	..	4	–	–		
					At (2)	None	..	..	4	–	–		
25*	M	29	A	Ar (2)	....	None	16	9	4	–	2		Second test 6 weeks after treatment; at this time Art. v. lud. was 4 +.
			HF	Ar (6)	....	None	..	..	4	4	3		
				Ar (7)	....	None	..	..	–	2	2		
				At (6)	....	None	..	..	4	4	4		
				C (2)	....	None	..	..	iv	–	–		
				S (1)	....	None	..	..	4	4	4		
					At (3)	None	..	..	3	–	3		
27*	M	34	HF	A (1)	....	None	15	14	4	–	4		
				C	....	48	..	..	4	–	4		
				F	....	None	..	..	4	–	–		
					A	None	..	..	4	4	3		
					A (3)	None	..	..	4	4	3		
					Ar (2)	None	..	..	3	4	3		
					At (1)	None	..	..	3	–	–		
					F (1)	None	..	..	4	2	–		
33*	F	35	HF	Ar (7)	....	20	15	12	iv	–	–		
			U	C	....	54	..	..	neg	–	–	neg	
				F	....	20	..	..	iv	4	4		
					A (1)	20	..	..	iii	4	4		
					Ar	None	..	..	iii	2	3		
					Ar (6)	None	..	..	iii	–	–		
					At (3)	None	..	..	iii	–	–		
					F (1)	None	..	..	iv	–	2		
34*	M	32	A	A (1)	....	None	15	5	3	–	4		
			HF	Ar (6)	....	None	..	..	3	–	–		
			U	At (1)	....	None	..	..	4	–	–		
				C	....	None	..	..	4	4	4		
					At	None	..	..	4	3	3		
40*	M	45	HF	Am (1)	....	None	15	9	?	4	4	iv	
				A (1)	....	None	..	..	4	3	3		
				Ar (7)	....	None	..	..	–	–	–		
				At (1)	....	None	..	..	4	2	–		
				F	....	None	..	..	4	2	3		
				X	....	15	..	..	4	2	–		
					Ar (2)	None	..	..	–	–	–		
					At (2)	None	..	..	4	–	4		
46*	M	33	HF	A (1)	....	15	15	14	3	4	4	4	
				Ar (1)	....	15	..	..	–	–	4	4	
				Ar (6)	....	None	..	..	–	–	3	4	
				At (1)	....	15	..	..	–	–	3	4	
				C	....	60	..	..	4	4	4		
				F	....	15	..	..	4	–	–		
					At	None	..	..	4	–	–		
					F (1)	None	..	..	4	–	–		
51	F	12	A	A (1)	....	31	15	12	neg	–	3	..	First test 4½ weeks after last treatment; second test 6½ weeks after treatment.
			HF	Ar (6)	....	28	..	..	neg	–	4		
				At (5)	....	25	..	..	ii	–	4		
				C (1)	....	15	..	..	neg	–	3		
				C	....	92	..	..	iv	–	3		
				F	....	25	..	..	neg	3	3		
					Ar (2)	None	..	..	iii	3	4		
					At (1)	None	..	..	iv	3	2		

* Indicates that to at least two pollens, but not to all, the skin reactions are negative at two, and often three, of the tests. In some instances the individual has never been positive to the pollens in question.

NOTE.—Tests made by the scratch or dermal method are indicated by "neg" or roman numeral ii, iii or iv.
Tests made by the intracutaneous method are indicated by "–" or arabic numeral 2, 3, 4.
If a test was not made at any of the three examinations the interrogation mark "?" is used.
Diagnoses are indicated by key letters: A = Asthma; HF = Hay fever; E = Eczema; U = Urticaria.

The first factor we wish to emphasize on the basis of the data presented is the change produced in the skin reaction to pollens used in treatment after the usual course of injections. In the great majority of these cases, the reaction is definitely decreased when the results of the two and four weeks' test are compared with the reaction obtained just prior to commencing preseasonal treatment. Note especially Cases 3, 8, 9, 12, 16, 17, 22 and 24. It would appear to us that skin desensitization is brought about more readily to the so-called fall pollens than it was to the spring pollens.[1] In several instances, only one or possibly two pollens of the three or six in the antigen will become skin-test negative, as illustrated by Cases 9, 10, 12, 21, 22, 25, 27 and 33. An occasional case is found where the reverse is true, namely, the skin reactions will become negative to all but one or possibly two (9, 22 and 33) of the pollens in the antigen. The reaction to Bermuda grass tends to be more persistent than any other one pollen. These findings may be considered presumptive evidence in favor of some degree of specificity of these reactions, but this will be referred to again.

The periods of two and four weeks after treatment were arbitrarily selected for the time of making tests. It has been claimed that clinical desensitization does not persist for a period in excess of a month or two after treatments have ceased. In this connection it is of interest to study the skin reactions in those cases in which the results of tests at two- and four-week periods are not in accord. In 16 cases (examples 9, 27, 46 and 51), two or more pollens were definitely more positive at the four- than at the two-week period, and in the majority of these the reaction had returned to what it was before treatments. In 4 (25 per cent) of these cases the last test was actually more than four weeks after treatment. From this, then, it

The pollens tested are indicated by key letters which have the following significance:

Key letter.	*Botanical name.*	*Common name.*
Am (1)	Amaranthus retroflexus	Rough pigweed.
A	Ambrosia artemisiaefolia (elatior)	Eastern ragweed.
A (1)	Ambrosia psilostachya	Western ragweed.
A (3)	Ambrosia trifida	Giant ragweed.
Ar	Artemisia biennis	Biennial sagewort
Ar (1)	Artemisia californica	Coast sagebrush
Ar (2)	Artemisia campestris pycnocephala	Field sagewort
Ar (3)	Artemisia dracunculus	Dragon sagewort
Ar (6)	Artemisia tridentata	Sagebrush.
Ar (7)	Artemisia vulgaris heterophylla	Mugwort.
F	Franseria acanthicarpa	False ragweed.
F (1)	Franseria bipinnatifida	Sandbur
F (2)	Franseria chamissonis	
X	Xanthium canadense	Cocklebur.
X (1)	Xanthium spinosum	Spiny cocklebur.
At	Atriplex argentea expansa	Silverscale.
At (1)	Atriplex bracteosa	Bractscale.
At (2)	Atriplex canescens typica	Wingscale.
At (3)	Atriplex lentiformis	Lenscale.
At (5)	Atriplex polycarpa	Allscale.
At (6)	Atriplex rosea	Redscale.
C	Cynodon dactylon	Bermuda grass.
C (1)	Chenopodium album	Lambsquarters.
C (2)	Chenopodium ambrosioides	Mexican tea
C (3)	Chenopodium murale	Nettle-leaved goosefoot.
S (1)	Salsola kali tenuifolia	Russian thistle.

may be suggested that skin desensitization, if obtained, tends to persist at least two weeks after treatment, although it may disappear in four to eight weeks. In the majority of instances, however, the desensitization persists at least four weeks. This and the previous study likewise present significant data which show that in some individuals the skin desensitization persists for a period of months or years, thus in the total of 64 cases numerous instances may be found in which the reaction before and at the two- and four-week period after treatment was negative. Many of these patients have previously been strongly positive—often more than twice—to the pollens in questions. That such desensitization does not represent a general loss of reactive capacity of the patient's skin to all pollens is indicated by the fact that these individuals may be negative to one pollen at the three tests indicated and yet strongly positive to several others at the same tests. This would likewise appear to be evidence in favor of the specificity of these reactions.

It has been claimed by Kahn,[2] though no data were submitted, that skin desensitization to grasses likewise brings about a skin desensitization to ragweed, even though the patient was strongly positive to both grasses and ragweed previous to spring (grass) treatment. We have a few cases, represented in the previous study,[1] in whom grass desensitization was accomplished who were also sensitive to fall pollens. These individuals received the regular fall retest on the same date that they were being tested to their grass pollen antigen either two or four weeks after treatment. The series is not large and no conclusions can be drawn, but it may be indicated that most of the cases failed to support Kahn's contention. This brings up the question of nonspecific skin desensitization and of group desensitization. An elucidation of this problem might throw some light upon the significance of skin reactions in diagnosis and prognosis. If a patient is equally sensitive to several pollens within a genus and one of these is more common in the patient's environment, he will be treated with this one and not with the others of this genus as it is assumed that treatment with one will protect him clinically against those with which he has infrequent contact. Let us see what evidence we have that such an assumption is borne out in the skin reactions. Each patient was tested after treatment to some pollens which had not been included in his antigen. In most instances, the pollen represented the same genera as those in his antigen, in a few cases he was tested with pollens from genera not even closely related to those represented in his antigen. The latter situation will be discussed in succeeding paragraphs. To return to the first point, there were 12 patients tested to species of Ambrosia, some of which were in the antigen, and some were not. Twenty-two were tested to Artemisia and 25 similarly tested to Atriplex. In the majority of these the skin reaction to members of any one genus were the same—either positive or negative—after treatment irrespective of

whether the pollen was in the antigen or not. As an example of all these findings 2 patients tested with Ambrosia have been selected. Case 17 was positive to Ambrosia psilostachya and Ambrosia elatior before treatment with the former. After treatment the reactions to both were negative. In Case 21 both Ambrosiæ tested were strongly positive before and even after treatment. It is of interest to note in passing that this latter case did become negative to an Atriplex as a result of treatment with it. The tendency is definitely toward skin desensitization of all members of a genus if it is accomplished for the one used in treatment.

The second point to consider is the effect upon the skin reaction of a fall pollen when no member of this particular genus was included in the treatment antigen. There are 16 cases with 20 observations which apply to this phase of the problem. In 15 of these observations the skin tests were definitely less at two and four weeks after treatment even though the pollen itself, or a member of the genus which it represents, was not used in treatment. Some of these pollens were members of a genus closely related to those represented in the antigen, and others were widely separated botanically from those employed in treatment. These facts coupled with the one that a polyvalent antigen was used in treatment make one cautious about too sweeping deductions, although possible interpretations will be given later.

The duplication of intracutaneous tests will be emphasized in another publication now in preparation.[3] In the above table, however, one may find examples in which the test at two and four weeks after treatment checked exactly. Such duplication seems especially significant when one considers that a period of at least two weeks elapsed between these tests. Furthermore, these duplications were obtained on cases which were not uniformly strongly positive or definitely negative (9, 10, 12, 21, 22, 33) to all pollens tested. We have previously determined[3] that a patient may react to one species of pollen and not to any other within the genus, or to several species in the same genus but to none of a closely related genus. In about 50 per cent of the total cases (those marked with an asterisk are examples) it may be noted that one or more pollens gave negative skin reactions in duplicate or even in triplicate even though strongly positive to other members of that genus or of a closely related one, thus supporting our previous contention that a skin sensitive individual does not necessarily react to all pollens. We wish to emphasize again that these findings are evidence of the specificity of the intracutaneous test and "a priori" of the reactive substance in the pollen extract and lastly of the response of the patient's skin.

Not infrequently the history of an allergic patient will implicate some pollen to which the individual is consistently skin-test negative. In spite of such negative reactions, it may seem advisable to employ this pollen in treatment. The possible effects of such a procedure

have been discussed.[4] Many of the cases reported in this study have been thus treated with a pollen to which a positive reaction has never been obtained, often in spite of several other courses of treatment with the same pollen (Cases 18 and 33). In the vast majority of these the reactions continued to be negative after this course of treatment even though the individual may still react positively to other pollens. Thus it is evident that our statements concerning the difficulty of inducing a positive skin reaction to a certain spring pollen even though the individual was hypersensitive to other spring pollens also holds for the fall pollens.

Summary. All discussions in this study concerning sensitivity or desensitization apply solely to the skin reactions. We make no attempt herein to correlate the skin sensitizations with the clinical ones or with the clinical results of treatment. It is admitted that it would be highly desirable to be able to directly correlate these phenomena and especially to be able to prognosticate on the skin test alone.[5] There may be some direct relationship between the degree of clinical and skin sensitivity, but the two factors do not always run parallel. It does appear to us that the general tendency is for the skin reactions to become less positive the more seasons the individual is under treatment. This phase will be studied later. In the face of variable and uncontrollable factors affecting the clinical condition of the patient, and to a less extent the skin reaction, it seems most logical to attempt to standardize one before theorizing on the relationship of one to the other. Therefore, we are attempting to indicate the variations and peculiarities of the skin tests, and if these can be foretold with sufficient accuracy it may then be possible to interpret them in terms of clinical factors.

Skin desensitization to pollens when no member of the genus they represent was used in treatment has been demonstrated. It may be claimed that this is evidence of a nonspecific or group desensitization. Had it been possible to carry out all these tests with various concentrations of pollen extract instead of a 1 to 1000 solution only, quantitative differences, not now evident, might have been demonstrated. Until further data are available it seems advisable not to attempt any theoretical explanation of this phase of the problem.

Conclusions. 1. Skin desensitization to fall pollens results in a majority of cases after the usual course of pollen treatments. A similar phenomenon has already been demonstrated for spring pollens.

2. In general this desensitization persists for at least four weeks and in some cases for months or years. In not a few cases, however, the desensitization begins to disappear before or shortly after the fourth week following treatment.

3. Factors which are considered evidence of the specificity of the skin reaction are pointed out and include: duplication of results at a two-week interval, presence of consistently negative reactions in a

patient who is strongly positive to closely related pollens, and the desensitization to one pollen and not to several others, or *vice versa*, as a result of treatments.

4. Treatment with a polyvalent antigen, if it decreases the skin reaction at all, decreases it to closely related species and in many instances to pollens which are members of genera not represented in the treatment antigen. There is some tendency for the skin to become negative to all fall pollens or to none of them.

5. The failure to engender skin reactions to certain pollens by injection of them into a person definitely skin hypersensitive to other pollens is noted for fall as it was previously for spring pollens.

6. Correlation of skin reactions with clinical factors is not attempted in this study, but the data have been analyzed in an effort to elucidate the phenomena connected with skin reactions.

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TWO CASES OF PERIPHERAL NEURONITIS RESEMBLING LANDRY'S PARALYSIS.

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PHILADELPHIA.

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The two cases here recorded illustrate the difficulty in differentiating, in some instances, involvement of the peripheral nerves from involvement of their central origins. They also bear out the well-known fact, realized for the first time some years ago by Mills, that the entire peripheral neuron, the cell and its processes, may be involved at the same time. In either instance, a diagnosis of symmetrical multiple neuritis with cranial nerve involvement might have been endorsed but the clinical manifestations point to the obvious incompleteness of such a diagnosis. On the other hand, if either had terminated fatally at the height of the illness, and there was grave likelihood of at least one doing so, the presumptive

diagnosis, Landry's ascending paralysis, would have been verified clinically, although equally incomplete.

Case Reports. CASE I.—An apparently toxic process of uncertain origin.

History. Miss H., aged forty-eight years, was admitted to the Infirmary for Nervous Diseases on July 17, 1926. She had been an extremely active type, enjoying the best of health until eight months previous to the onset of this illness. At that time for a period of three weeks there was a persistent, copious water discharge from the nostrils and eyes, accompanied by frequent spells of sneezing, especially in the mornings. The exact nature of the disturbance is unknown but after the subsidence of the discharge she did not return to her former status of health. She lacked her former endurance and easily tired; everything attempted was an extreme effort. She continued with her usual activities until July 7 when a tingling sensation in the feet was noticed, a feeling of "being asleep."

Frequent massage, bathing and dancing about were ineffective. She continued at work for the next two days, in spite of a gradually developing weakness in the legs. They felt heavy and clumsy and walking became increasingly difficult. Five days after the onset of tingling the knees sagged and she had to be carried to bed. At this time the same process became apparent in the upper extremities, that is, tingling sensations in the fingers and hands with weakness. Sharp shooting pains were experienced in the legs and a sensation of a belt around the chest impeding respiration. She had to be raised on a pillow to facilitate breathing.

Physical Examination. Nine days after the onset she was profoundly prostrated but the sensorium was clear and the temperature normal. The neck was slightly stiff and Kernig's sign was present.

Cranial Nerves: There was limitation of external rotation of the eyes, bilateral weakness of the masseters, loss of corneal and orbicular reflexes and a bilateral peripheral facial weakness more severe on the left side. There was an ulcerative keratitis on the right, probably because of the exposure due to the seventh cranial-nerve weakness or because of implication of the vegetative fibers of the fifth nerve sheath. The right eye also showed some congestion and edema of the conjunctiva and an iritis, probably secondary to the keratitis. A milder degree of keratitis was present in the left eye, the cornea lacking the normal luster.

The breathing was difficult, resembling the Cheyne-Stokes type, the heart action weak and erratic, and there was difficulty in swallowing and impairment of the activity of the tongue. It was necessary to resort to rectal feeding.

There was a flaccid, symmetrical paralysis of all the extremities, with total loss of tendon reflexes. She could move the toes slightly and slowly pronate and supinate the hands, but all other movements were lost. Wasting of the musculature was general, well marked and symmetrical. No fibrillary twitchings were noted.

Sensory examination showed extreme tenderness to light and deep pressure and to passive movement over the limbs and trunk. No other objective sensory disturbances were noted, excepting the corneal analgesia. The subjective findings consisted of the paresthesias of the onset and the shooting pains in the lower extremities.

The cerebrospinal fluid was faintly opalescent and yellow with a cell count of 53 per c.mm., 92 per cent of which were lymphocytes. The Pandy reaction was strongly positive, the Wassermann reaction negative and the colloidal-gold curve absent.

Other laboratory findings included normal blood findings, while the urine showed a trace of albumin and a few hyaline casts.

Course: At this critical stage she was presumed to have a typical ascending Landry's paralysis and was instructed not to make the slightest physical effort. A serum was prepared from the blood of an old case of poliomyelitis and injected intraspinously on three occasions. This may have been a factor in her recovery. The process maintained its height from the ninth to the thirteenth day after which it began to slowly subside in an unfolding manner. The keratitis and the cranial nerve manifestations were the first to mend, followed closely by returning power in the arms and legs. In addition to the cranial nerve symptoms already mentioned it was interesting to note, after the clearing of the keratitis made a fundus examination possible, a papillitis of one diopter. The cause of this complication is uncertain. It is not mentioned in the literature of poliomyelitis, but can occur, it is stated, in the wake of a multiple neuritis.

Within three months the arms were normal excepting for some remaining wasting and weakness of the shoulder muscles. The lumbar muscles remained involved, causing difficulty in sitting up and there was considerable atrophy and weakness in the lower extremities.

Five months after the onset, she was entirely recovered with the exception of a slight diminution in power of the peroneal groups of muscles. All tendon reflexes had returned except the Achilles. This reflex returned and the muscular weakness was overcome within a few weeks.

Case II.—A similar apparently toxic process of unknown origin.

History. Mr. K., a traveling salesman, aged twenty-seven years, had been free of any illness since childhood until July 4, 1926, when he noticed a numbness of the feet and legs with sagging of the knees. By July 15 he was unable to stand and was forced to go to bed. Two weeks later there developed gradually weakness of the arms. At this time four weeks after the onset he was admitted to the Infirmary for Nervous Diseases.

Physical Examination. August 1, 1926. Cranial Nerves: The muscles of mastication were weak and tender and there was weakness over the left side of the face. Swallowing was difficult because of a feeling of thickness in the throat. Breathing was shallow and rapid and there was a sensation of constriction about the chest. The pulse was accelerated and weak. A fine tremor of the tongue was noted and an impairment in its motility. He was unable, for instance, to remove fragments of food lodging between the teeth.

Extremities: In the lower all movements were lost except for the toes and a slight flexion of the thighs. There was flaccidity and loss of tendon reflexes. The upper extremities were symmetrically but less decidedly weak with flaccidity and lost tendon reflexes.

The musculature showed general wasting and hypotonicity of the extremities and trunk and occasional fibrillary twitchings about the upper back, shoulders, forearms, hands and inner parts of the thighs.

Sensory findings were limited to tenderness to deep pressure over muscles, joints and nerve trunks; impairment of the sense of position in the toes; and loss of the appreciation of vibration in the lower extremities as far up as the iliac crests. Touch and temperature were unimpaired as were two-point discrimination and the recognition of similarity and difference in objects coming into bodily contact.

Laboratory findings were as follows: The spinal fluid showed a negative Wassermann and cell counts, on five occasions from August to October, 1926, of 15, 27, 129, 3 and 4 per c.mm. The blood was normal and the urine contained a trace of albumin and a few hyaline casts.

Electrical Reactions: On September 1 the response to galvanism and faradism in the leg muscles and the biceps of the arms was much less than normal, but there was no reaction of degeneration. On October 6 and

December 6, the reaction of degeneration was present in the muscles of the legs and the biceps of the arms, but the faradic current still gave a response.

Course: He received repeated intraspinal injections of the serum of the first case but was unimproved after two weeks at the infirmary. The constriction about the chest made breathing a little more difficult, the abdominal muscles seemed weaker and the pulse increased in rate to 124 and the respirations to 20. He was generally weaker and could not raise the arms or elevate the lower extremities. At no time was there fever.

Within two months, he began to improve. The muscles of mastication and the facial and tongue weakness were the first to clear, followed closely by relief of the feeling of chest constriction. Gradually he came to make greater use of his arms and within another month was able to sit up.

In five months, there was considerable return of power in all extremities, but much wasting, persistent fibrillary twitchings and continued absence of all tendon reflexes. The sensory disturbances were improved; tenderness was limited to the soles of the feet and calves. Passive position appreciation had returned to the toes and vibratory appreciation to the entire lower extremities although somewhat impaired.

Within nine months, April, 1927, the arms had recovered almost their usual strength but there was evidence of slight atrophy and occasional fibrillary twitchings in the muscles of the hands and forearms were to be seen. The lower extremities were weaker and more wasted. He could walk about on a broad base with a steppage gait, but could not stand with the eyes closed. All tendon reflexes remained absent. Sensation had returned to normal excepting for a slight tenderness in the calves.

In July, 1927, the arms were normal in strength and no twitchings were noted. The lower extremities remained somewhat wasted and weak, especially the gastrocnemius and soleus muscles and the peroneal groups. He walked better but was unable to rise to his toes or heels. All tendon reflexes remained absent.

To date, October, 1927, he has almost recovered. There remain only a slight steppage gait and a slight weakness in the calf and peroneal muscles. He can rise on his heels but not on his toes. All tendon reflexes have returned except the Achilles.

Comment. The first case was apparently a true Landry's ascending paralysis with recovery, while the second might be termed a symmetrical ascending polyneuritis with cranial-nerve involvement. Still, they were very similar, differing mainly in degree of intensity and in the time elapsing in development and recovery. Both began in the same manner in the peripheral nerve fibers, involving not only the terminal branches but also the trunks, roots, and most likely, their central cell origins but not to the point of destruction.

It is not reasonable to suppose that a toxic or infectious process could be expected to limit its involvement to any one anatomic portion of a neuron, whether beginning in the terminal fiber, trunk, root or cell. There must be overlapping or extension by contiguity to some extent. If the process begins as a terminal neuritis, as it seems to have done in these cases, the extension must tend to overlap in the direction of the central cell.

In poliomyelitis, the anterior horn cells are usually affected to the point of destruction, but the process is not definitely limited to this particular area because we commonly have pain, a sensory mani-

festation. This pain may be due to irritation of the posterior root zone within the cord but is usually the result of meningeal irritation of the posterior roots without the cord.

In the first case, in addition to the signs of peripheral-nerve involvement, there were pain and tenderness over the whole body with a stiff neck, Kernig's sign and a papillitis, all indicative of meningeal involvement. The spinal-fluid findings tended to corroborate, in as much as it contained a large amount of protein, had a very slight yellowish tinge, an absence of a colloidal-gold curve and a cell count of 53 per c.mm.

In the same manner both processes might be assumed to have originated as toxic or infectious involvements of the peripheral nerves. The rapidly progressive, symmetrical, ascending, flaccid paralysis with cranial-nerve implication; the marked atrophy; the fibrillary twitchings and changes in electrical reactions in one; the meningeal signs in the other, including the spinal-fluid findings; all these factors point to a general involvement of the entire peripheral motor neuron, the central cells included but not sufficiently so to cause destruction and permanent damage.

Summary. The question as to whether the term peripheral neuronitis is of any special value is not so much to be considered as are the clinical possibilities in toxic or infectious processes originating in either the peripheral nerve fiber or its central origin.

FACIAL DIPLEGIA.

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There is, perhaps, no better illustration of the slowness, as well as the difficulty in acquiring medical facts than is shown in regard the etiology of the peripheral type of facial paralysis. It was over a hundred years ago that Charles Bell, in the Philosophical Transactions of The Royal Society of London, first discussed the subject.[1]

At that time the facial nerve was considered as a nerve taking part in the respiratory act, and experiments were performed which showed that in dogs and horses it served as the principal motor nerve to the face. It was called the Portio dura nervi acustica. However, Bell's phenomenon, so called, refers to that particular phase of a peripheral type of facial paralysis in which the patient will rotate the eyeball upward and outward on unsuccessfully attempting to close the eyelids.

For many years, the commonly accepted cause for this disease, either unilateral or bilateral, was overexposure to cold in one particularly susceptible to affections of the nervous system. There

are still those who may believe that cold may be the sole cause of the disease, but the majority agree with Patrick and others who think there is infection elsewhere plus exposure to cold. There are those who so strongly advocate the idea of focal infection elsewhere as being the cause of peripheral facial paralysis that they recommend the removal of suspected tonsils, teeth, and so forth, during the course of the disease. Good results are said to have been obtained, and the length of time the patient suffered from the paralysis was thought to have been shortened.[2]

It would seem, however, that the disease would lend itself to a systematic classification as regards etiology, such classification being applicable in either bilateral or unilateral type. One must consider the following causes:

1. Congenital Defects. (*a*) Absence of nucleus or nerve peripheral to the nucleus; (*b*) defect of bony canal through which the nerve passes.

2. Infections. Infections at the site of the lesion by: S. pallida, especially in the secondary and tertiary stages, tubercle bacillus, meningococcus, streptococcus, staphylococcus, pneumococcus, Pfeiffer bacillus; also the organisms of multiple neuritis and ganglionitis, occurring either separately or in association with each other or with acute epidemic encephalitis.

Some may occur by extension, as in otitis media, mastoiditis, and caries of the bony canal from infective disease of the bone itself.

3. Toxic. (*a*) From infection elsewhere, as in: (1) Acute and chronic tonsillitis, pharyngitis, rhinitis, sinusitis, and Pyorrhea alveolaris. Some might consider the latter as a questionable cause, yet there is evidence enough that chronic infection about the teeth and gums can cause ganglionitis and herpes zoster. From the bacteriological standpoint these include all the respiratory organisms such as streptococcus, staphylococcus, pneumococcus, influenza, diphtheria, and so forth. (2) One might add here such diseases as typhoid, acute contagious diseases, and certain diseases in which there occurs a bacteremia such as puerperal septicemia, acute rheumatic fever, and the purpuras. However, until a more careful study is made of the spinal fluid in these cases, it is questionable as to whether they are toxic or infective at the site. (*b*) Toxic, as in: (1) Drugs (alcohol, lead, arsenic, mercury, salvarsan); (2) metabolic diseases (gout, diabetes, and so forth—Oppenheim); (4) toxemias of pregnancy.

4. Trauma. (*a*) Operative procedures, particularly around the mastoid; (*b*) puncture wounds, gunshot, and stabbing; (*c*) skull fractures and resultant intracranial hemorrhage and edema; (*d*) vascular accidents (hemorrhage, ruptured aneurysm) in neighborhood of nucleus or nerve; (*e*) birth injuries (intracranial, extracranial); (*f*) pressure—from tumors elsewhere (pons, medulla, along

the bony canal, or in the parotid region); from carotid aneurysm (as in a case under my observation at present).

The medical literature at the present time contains numerous articles which deal directly and indirectly with cases of facial paralysis, either unilateral or bilateral, and whose etiology is closely associated, if not identical, with that of epidemic encephalitis.

Since the beginning of the recent epidemic of encephalitis, there has been, and still is, considerable confusion in the minds of many as to whether they were dealing with cases of multiple neuritis, associated with a certain degree of myelitis and encephalitis, or as to whether the encephalitis should be given prime consideration, particularly from the prognostic standpoint. The bacteriologic study of acute polyneuritis and epidemic encephalitis has not served as yet to solve the problem, and no small amount of time has been given to it. Evans and Freeman, in a recent study on the etiology of epidemic encephalitis, found an organism which was identical with that isolated by von Wiesner and by Rosenow.[3] They state: "The remarkable pleomorphism of the organism suggests life cycles as complex as those of some of the higher fungi. It may be stated briefly that, in one of the phases of its life history, this organism is a spore-forming rod. The rod form produces not only spores but also exceedingly minute filtrable, coccoid bodies, which develop on the outer walls of these rods. Under certain conditions, these minute coccoid bodies enlarge and multiply as cocci." They promise further reports.

The fact that the organism goes through complex life cycles suggests the possibility of varied symptomatology according to seasons. Individual susceptibility, as well as organ susceptibility, must also be considered.

Bradford, Bashford, and Wilson[4] made a thorough study of 30 cases of acute infective polyneuritis occurring in soldiers during the World War and found facial diplegia in practically all of their cases. They reported a high rate of mortality, 8 in 30 cases. In view of the fact that intensive study of epidemic encephalitis was just beginning and considering the almost universal facial diplegia found, as well as the actual report of lethargy in 1 case, one realizes the difficulty then, as well as now, in accurately classifying some of these cases.

They were able to culture the organism from the cerebral cortex and also from the spinal fluid, and they discussed at some length the similarity of the organism in morphology and staining reactions to that of anterior poliomyelitis as reported by Amoss[5] and Smillie.[6]

The spinal-fluid examination in all of the 30 cases reported by Bradford showed practically no change from normal. Likewise, in the 12 cases reported by Gordon Holmes no change in the fluid was noted.[7] In a recent case reported by A. B. Yudelson the spinal fluid was not examined.[8]

The following 2 case reports are interesting and instructive in that the first one is typical of a facial diplegia in acute polyneuritis, while the second case illustrates the difficulty encountered in differentiating the above condition from myasthenia gravis.

The first case showed spinal-fluid changes similar, in some respects, to those reported by Viets[9] in that the albumin and globulin content was increased and the gold curves were quite similar. He found that the protein content "may be increased to ten, or more, times normal, without other changes in the fluid." The pupillary changes, transitory attacks of double vision, and the spinal-fluid findings are suggestive, if not diagnostic, of an associated encephalitis. Most authors who have written recently on this type of infection, usually called acute polyneuritis, feel that the term "neuronitis" or "polyneuronitis" is more nearly correct.

Case Reports. CASE I.—Referred by Dr. Lyman of Grand Rapids, Mich. Miss L. K., a teacher, aged twenty-five years, complained of inability to move the muscles of her face and of weakness of all her extremities. Her family history was negative. The past history and menstrual history were negative, except for influenza in 1918.

Present Trouble. In November, 1924, the patient had an acute rhinitis followed by bronchitis. She was not incapacitated, but went to her physician who found no evidence of diphtheria. She recovered in a few days. In early December, 1924, she was given an inoculation to prevent "colds," and she was not certain but what she may have had a slight cold at the time. On December 25 she noticed aching in the legs, which kept her awake nights. By December 31 she noticed numbness of the anterior part of the right foot and a peculiar numb sensation of the left side of the face. On January 2 she was unable to move the muscles of the right side of the face. January 7 the left side of the face was similarly involved. Later, the left foot, and sometimes the left leg, became numb, and only by looking at them could she tell their location. She had a "drawing-up" sensation in the toes and aching in the legs at night, which caused sleeplessness practically all during her hospital stay (January 8, 1925 to January 29, 1925). She also complained of tingling in fingers, although the hands and arms were never involved to the same extent as the legs. She had ringing in the ears and blurring of vision in the right eye at times. Occasional double vision and difficulty in closing the lids. She had difficulty in eating, but none in swallowing. Never any regurgitation of food. Marked general feeling of lassitude. No intestinal nor bladder symptoms. Her highest temperature was 99.4°, and pulse ranged from 90 to 120. Respirations, 20 to 25.

Examination. Mentally, the patient was normal in every respect throughout her illness.

The gait and station were not tested because of the weakness in the lower extremities. She had no tremors and no ataxia on finger-to-nose test. No atrophies nor deformities. Hair was unusually gray, considering her age. Her skin was pale and sallow. Memory and speech, normal in all respects. She had no definite paralysis in any of her extremities but a marked generalized weakness, especially in the lower extremities.

Cranial Nerves. She complained of double vision at times, but the extraocular movements, to gross tests, were normal. The pupils were equal, round, and symmetrical. They reacted promptly to light and in accommodation. There was no nystagmus. The sclerae were clear. She had a definite bilateral facial paralysis, including the usual signs of the peripheral

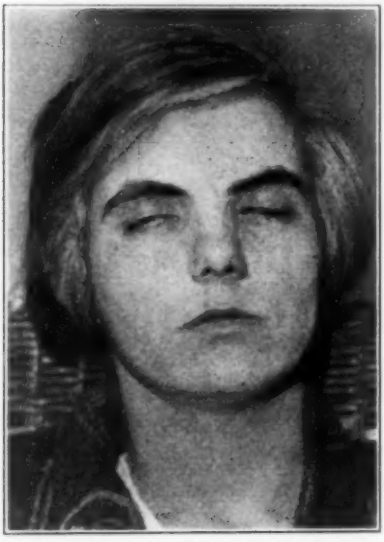

FIG. 1.—Case I. Facial diplegia in multiple neuritis. Patient attempting to close the eyes.

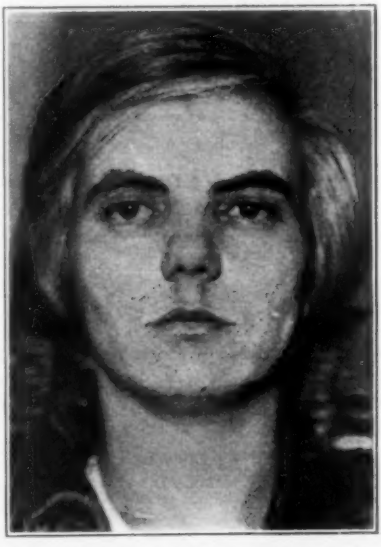

FIG. 2.—Case I. Facial diplegia in multiple neuritis. Patient was asked to draw back the corners of her mouth, as in smiling.

FIG. 3.—Case I. Facial diplegia in multiple neuritis. After partial recovery, showing the inequality of the lower facial muscles.

FIG. 4.—Case I. Facial diplegia in multiple neuritis. After partial recovery, patient attempting to wrinkle the forehead.

type. She could not wrinkle the forehead on either side, and she could not close the eyelids. The left palpebral fissure was narrower than the right. She could not smile. Food would collect between the teeth and sides of the mouth when eating, necessitating manual removal. Tongue and jaw movements were normal. Swallowing was normal. Taste was normal. There was no regurgitation of food through the nose. The palate movements were normal. During the hospital stay, she could read by closing one eye.

Deep Reflexes. Biceps, triceps, knee, and Achilles were not obtained.

Sensation. She had some disturbance of sensation to motion and position, pain, and light touch in the lower extremities and also to a slight extent in the hands. There were indefinite areas of hyperesthesia and anesthesia in the lower extremities especially. She complained of her feet being "heavy like wood." She also complained of a ringing in her ears. Sensation on the face and body was normal. She had marked pain in the lower extremities during the first few days of her hospital visit.

FIG. 5.—Case I.—Facial diplegia in multiple neuritis. Normal appearance of face after partial recovery. Compare with Fig. 2.

Laboratory Examinations. Urinalysis (January 10): Clear, straw-colored, specific gravity, 1.019; reaction, neutral; no sugar nor albumin; leukocytes 2 +. Blood (January 8): Leukocytes, 10,650; erythrocytes, 4,140,000; hemoglobin, 85 per cent (Sahli). Differential: Number of cells counted, 100; polymorphonuclears, 66; small lymphocytes, 21; large lymphocytes, 9; transitionals, 1; esophinophils, 1; basophils, 2; Wassermann test, negative. Spinal fluid (January 8): Clear, colorless; cells per c.mm. 32 (all polymorphonuclears); carbolic, 3 +; N. A. No. 1, 2 +; N. A. No. 2, 3 +; Fehling's test, normal; sugar, 0.09; gold curve, 001223311000; Wassermann, and microscopic culture, negative.

Progress Notes. The patient remained in the hospital about twenty days, and gradually improved. The left side of the face began to improve first. Within a few days, she was able to move the muscles of the lower face, close her left eye, and wrinkle the forehead to a slight degree. The sleep-

lessness which she experienced during this time was due mostly to pains and paresthesias in the lower extremities. After entering the hospital, the right leg became much worse until she was finally unable to move it in any direction. It began to show slight signs of improvement a few days before leaving the hospital.

Her improvement during February, March, and April was rather rapid, and she was able to resume her work at teaching during the months of May and June.

She returned for reëxamination in July. At that time the right side of the face showed deeper wrinkling than the left, suggesting contracture. She was still unable to wrinkle the right side of the forehead. Her left pupil was larger than the right, and it did not react so promptly as the right to either light or accommodation. The right Achilles and the right knee reflexes were absent, while the left Achilles and the left knee reflexes had returned. The toe nails showed a horizontal ridging half way across each one, corresponding to the degree of regeneration which had taken place. She was hypersensitive to pin point and light touch in both feet and legs, while the vibratory sense was less acute in the right ankle than in the left. Sensation of motion and position was normal.

The patient again returned April 1, 1926. At that time she stated that she would occasionally see double. The pupils were about equal when dilated, but when contracted the right was definitely smaller. She gave a history of having one or two head colds, but she did not associate them with the double vision. The right knee reflex was now present on reinforcement, but the other deep reflexes were as before.

She returned April 11, 1927. The patient still complains of being unable to wrinkle the right forehead and of a stiffness in movements about the right eye and also in the movements of the right side of the face. She complains of some cramping in the toes of the right foot. The condition of the facial muscles and the pupils remained the same. The right knee reflex was present without reinforcement. She is still hypersensitive to pin point. The other sensory tests were within range of normal.

Treatment. The patient's pain was controlled by sodium salicylate during her hospital stay. She was given hypodermics of sodium cacodylate, 3 gr., every other day, and heat was applied to the affected parts. No massage was used until after the first fourteen days of her illness. Later, both massage and passive exercises were used, and the patient seemed to gradually improve. No other medication was given except syrup ferri iodid and elixir I. Q. & S. Later, the patient was placed in the care of a physiotherapist, who gave gentle massage to the right side of the face and applied mild faradic current. She also instructed the patient in muscle training.

As will be noted by the above examination, the patient has as yet shown no signs of developing postencephalitic changes either in a mental or physical way. Her general health and weight has improved.

Case II.—Mr. J. C. V., bookkeeper, aged twenty-five years, was referred by Dr. Carl Snapp of Grand Rapids, Mich.

The patient complained of inability to move his lips properly and to "blow out his cheeks." He could not close his eyes nor wrinkle his forehead. Food regurgitated through his nose. Aside from a marked family history of tuberculosis, there were no particular familial diseases. His past history was negative. He had no history of scarlet fever nor diphtheria but he gave a history of having, as a child, otitis media every winter until ten years ago. He had an incomplete tonsillectomy and adenoidectomy

FIG. 6.—Case II. Myasthenia gravis. Patient attempting to puff out the cheeks.

FIG. 7.—Case II. Myasthenia gravis. Patient attempting to close the eyelids and to draw back the corners of the mouth.

when three years of age. He also had a partial nasal obstruction for as long as he can remember. He denied venereal disease.

About two months ago (November 22, 1926), the patient had a head cold, which, as he described it, kept hanging on. He had a continual nasal discharge, but no cough nor sore throat in connection with the rhinitis. No diphtheritic membrane and no remembrace of any chill or fever with the cold. He had no blurring of vision.

About two days ago, on January 20, 1927, he noticed for the first time the inability to close the eyes and to wrinkle the forehead. He also noticed that he was unable to blow his cornet. He noticed that when he ate, food sometimes regurgitated through the nose and lodged between the teeth and his cheeks.

FIG. 8.—Case II. Myasthenia gravis. Patient attempting to wrinkle the forehead.

His examination showed a bilateral facial paresis. He was unable to retract the lower facial muscles, and he could not completely close either eye. He could wrinkle the forehead but very slightly and that on the right side only. The tongue movements were normal. The pinched expression of the nose was normal for him. The palate drew up better on the right side than on the left. The pupillary reflexes were all normal. The extra-ocular movements were normal. Both taste and smell were normal. All of the deep reflexes were present but somewhat sluggish. No Babinski. No clonus. Sensation to pain, light touch, motion and position, vibration, head and cold, and deep pressure were all normal. No electrical reactions carried out at this time.

Laboratory work was as follows: Urinalysis (January 23): Amber, clear; specific gravity, 1.030; acid in reaction; no sugar; albumin, faint trace; leukocytes, 10. Blood (January 24): Leukocytes, 8450; erythrocytes, 4,800,000; hemoglobin, 80 per cent. Differential: Number of cells counted, 100; polymorphonuclears, 66; small lymphocytes, 32; large lymphocytes, 2. Wassermann reaction was negative (January 25). Spinal fluid

(January 25): Description, clear, colorless; pressure, 2 +; cells per c.mm, 1; carbolic, negative; N. A. No. 1, negative; N. A. No. 2, negative; Fehling, normal; gold curve, 111221000000; microscopic, sterile; no acid-fast bacilli. Throat culture (January 23): Predominant organism, staphylococcus and pneumococcus.

During the first week of treatment, the patient was allowed to be up and around, and he came to the office where he was given three intravenous injections of sodium iodid. During the same time, he was also given ultraviolet light treatments, three in number. He gradually grew worse on the above treatment, and he was placed in the hospital for absolute rest. The light treatments were continued and sodium cacodylate, 5 gr., was given twice weekly. Previous to entering the hospital, he had developed some weakness in both arms, particularly in flexion and extension of the fingers of both hands. After about two weeks' stay in the hospital, the patient's tonsils were removed. He gradually improved following the tonsillectomy, and in a few weeks returned to his work.

The patient was not seen for a period of eight months, and in the meantime (June, 1927) he had developed a severe remission with absolute inability to swallow and marked generalized weakness. A gastrostomy operation, under local anesthetic, was performed at the Mayo Clinic, and this undoubtedly saved the patient's life. They made a diagnosis for the first time of myasthenia gravis, and the patient is still slowly improving from this last remission. He is unable to swallow, but he can read and carry on a conversation for a short time without particular fatigue.

Comment. This case illustrates the difficulty in distinguishing between a polyneuritis involving the bulbar and facial nerves and myasthenia gravis. Owing to the fact that the patient's first symptoms came on rather suddenly and were preceded by a definite head cold, a careful search was made for the diphtheria organism but without success. Later attempts following the operation (gastrostomy) were likewise unsuccessful. Each of his remissions, however, have been preceded by an acute nasal infection, even after removal of the tonsils. The adenoid expression, so typical of an advanced case of myasthenia gravis, was supposedly normal for this individual inasmuch as he had a rather definite nasal obstruction and a long history of adenoid enlargement as well as otitis media yearly until the age of fifteen years.

This patient, when first seen, had difficulty in closing the eyes rather than in opening them as is usual in myasthenia gravis, and his weakness of the facial, orbicularis oculi, and levator palpebræ muscles was without the usual marked variations related to fatigue until later in the disease.

Conclusions. 1. An attempt has been made to outline a working classification for use in cases of facial paralysis.

2. The difficulty of distinguishing between multiple neuritis with facial diplegia and some of the cases of acute epidemic encephalitis and allied conditions has been briefly discussed.

3. One case of facial diplegia in multiple neuritis is presented, which shows marked changes in the spinal fluid. The author has noticed no reports of other cases showing these changes except that

of Viets. The term "neuronitis," as suggested by others, is perhaps better than neuritis for this syndrome.

4. A case is reported which shows the difficulty in differentiating between polyneuritis and myasthenia gravis and which emphasizes the importance of testing for the myasthenic reaction to tetanization by the faradic current in suspected cases.

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MERALGIA PARESTHETICA.*

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This clinical syndrome, first described as an entity by Bernhardt[1] and again by Roth[2] in 1895, may be summarized as combining paresthesias, pain and some objective sensory disturbance, over the anterolateral surface of the thigh, usually extending nearly to the knee; it occurs more often in men, and may show a familial incidence. The affected zone varies from an irregular circle or oval to one of "snowshoe-shape" (Long and Mozer[3]). Subjectively, the common complaints are of numbness, coldness, burning, tingling, or pain; objectively, hyperesthesia or hypesthesia is demonstrable. Hypesthesia is usually most marked over the inferior part of the thigh. A painful point is often found just medial to the anterior superior iliac spine. Trophic disturbances of the skin may occur (less often than in causalgias). The pilomotor reflex is modified or lost.

There can be both pains and paresthesias without any objective

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change. Paresthesias are likely to lose intensity toward the periphery of the patch. The areas delimiting different types of sensory disorder do not necessarily exactly coincide. Altered sensibility may differ in the same case at different times, and in fact simple rubbing of an hypesthetic area tends to restore sensation temporarily. The subjective symptoms are aggravated by standing or walking; they may or may not persist when the subject is seated, but do disappear when the recumbent posture is assumed. The hypesthesias to superficial touch, pinprick, and temperature, do not progress to absolute anesthesia.

The condition may occasionally be bilateral rather than unilateral. In the pure form, it comprises sensory disturbances limited to the territory of the lateral cutaneous nerve of the thigh. In other forms, the areas of distribution of adjacent nerves, as the middle cutaneous, can be similarly affected. Further, there may be other neuralgias, as in one or both sciatic distributions. Typically, there is no change in deep reflexes or in motion.

The onset of the syndrome is insidious, abnormal sensations preceding real pains. The duration is a matter of years or decades, although *formes frustes* have been described, one case lasting as short a time as three months.

The lateral cutaneous nerve of the thigh, exclusively sensory, arises from the second lumbar root, a branch of the lumbar plexus, and leaving from the back of the psoas crosses the middle of the iliac fossa perpendicularly to the iliacus, passing out through a notch in the ilium medially to the anterior-superior iliac spine and toward the anterior aspect of the thigh, where it passes through a narrow fissure between the tendons of the tensor fasciæ latæ and the sartorius, anteriorly and medially to the latter. There, at a point 2 cm. from the iliac spine, the nerve divides into a cutaneous branch directed toward the buttock, which supplies the area about the great trochanter, and into one or two femoral branches that supply the antero-external surface of the thigh, from the trochanter sometimes as far as to the upper edge of the patella. Anomalies in the surface ordinarily affected are explainable both by inclusion of adjacent nerves in the disease process, and anastomoses of the lateral with the middle cutaneous, the genitocrural, and so forth. The branch to the buttock may be exclusively affected, but is commonly enough not involved with the rest of its nerve.

The accepted origin from the second lumbar root is qualified somewhat by Lapinsky,[4] who (quoting Eisler) comments on the nerve's occasional derivation, partially from the first and third lumbar segments as well as the second. A central disease process in one segment could then readily involve only a part rather than the whole of the lateral cutaneous nerve's distribution, and could as readily involve adjacent distributions—just as we are informed that it sometimes does.

As to Head's zones of hyperalgesia, the cutaneous territories of L2, 3 and 4 are considered to be unaffected in visceral disease. Behan[5] includes the lateral cutaneous among the nerves involved in pain referred from the kidneys, but does not specifically cite meralgia paresthetica in this connection. Langstroth[6] mentions a case of hyperalgesia covering the distributions of D6 to 12 and L2 to 5 inclusive, where spondylitis deformans was responsible.

The symptomatology, as described in different cases in the literature, may seem to embrace a range between that commonly associated with central pain, and that generally classified as causalgia. The conception here presented of the meralgic symptom complex is indeed intended to cover such a range. It would be quite as reasonable for purposes of classification to regroup the material along etiological lines of cleavage differing from those to be mentioned, or, possibly on a basis of various distributions of the symptoms. We shall group those cases in which the symptoms show a distribution strictly limited to part or all of the area supplied by the *Nervus cutaneous femoris lateralis*, together with those in which the affected area is bilateral or spreads on either side into the territory of adjacent nerves, such as the *Nervus femoralis*.

Taking the sensory path for pain as made up of three neurones—cell bodies of the first stage being in the dorsal ganglia, of the second in the dorsal horns of the cord or corresponding nuclei of the medulla and above, and of the third in the thalamus—the cell body of either stage may be affected by the two types of disturbance, *viz.*, partial or total destruction, and irritation. Destruction alone would effect a hypalgesia or analgesia, irritation alone a subjective sense of pain; but evidently the two will be combined in order to give rise to a hypalgesia dolorosa, or to a hypesthesia dolorosa, such as meralgia presents. Similar clinical pictures should result from lesions at quite different levels; however, a lesion of cell bodies at the third or thalamic level could scarcely give a sufficiently localizable symptomatology to be denominated meralgic.

The characteristics in common of central pain associated with lesions of these three neurones have been summarized as follows by Nicolesco.[7] This pain is burning and crushing in character; it is diffuse, not closely localized, and often both superficial and deep; it is persistent, with exacerbations, and peculiarly resistive to either physical or chemical forms of therapy; there may be accompanying vasomotor disorders. Although generally conceived of as based upon a peripheral abnormality, the picture of meralgia paresthetica may be practically indistinguishable from that of certain central lesions.

Meralgias may then be classified etiologically, both as to the nature of a causative lesion, and as to the site of its operation in the course of the first two sensory neurones. Osler[8] noted the apparent vulnerability of the nerve at Poupart's ligament, and Oppen-

heim[9] called attention to the possibilities of injury from pressure by the margin of the fascia lata. Flatfoot has been stated to be a frequent cause of the syndrome, and its associated abnormal mechanical conditions may be accountable for an irritative pressure or traction at the level of the fascia lata. Long and Mozer admit that participation in the movements of the tensor fasciæ latæ may cause variations in paresthesias, but argue nevertheless for an antecedent alteration in the nerve. That predisposition plays some part is indicated by the several familial cases reported. Obesity might also be associated with a constitutional predisposition. Another interesting suggestion has been offered by Lapinsky to the effect that shifting of this nerve in phylogeny from the gluteal region anteriorly to the thigh has a bearing on its vulnerability.

Trauma by a contusion or other wound of the trunk of the lateral cutaneous nerve of the thigh is a commonly assigned cause of meralgia. Thus the constant wearing of a sword was considered etiological for several cases reported in the earliest papers on the subject. Corsets and belts have sometimes seemed to traumatise the same nerve with similar results. One patient here presented suffered from a bullet wound of the upper thigh; the second was exposed to pressure from the edge of a table while at work. Trauma could act similarly at any point along the course of this peripheral nerve.

Trauma with its sequelæ within the central nervous system, affecting neurones whose cell bodies are located in the dorsal horns, could conceivably be such as to pick out a group including enough of the cells related to a lateral femorocutaneous nerve, to give at some time a meralgic picture—overlaid as it might be by motor complications.

Besides injuries caused from without the body, there are the possible pressures from other structures to be considered in connection with sensory neurones both of the first and second order.

Pressure on the nerve trunk may be exerted by intraäbdominal tumors, by the pregnant uterus (6 per cent in Musser and Sailer's[10] review of the literature in 1900), or by other enlarged or distended organs. Simple obesity is a frequently assigned cause. Pressure at the foramina, emphasized particularly by Rosenheck,[11] may arise from spondylitis of the upper lumbar vertebræ. André-Thomas[12] claims irritation at the distal end of the peripheral nerve, that is, at the terminal filaments, as the usual cause of the syndrome.

Pressure and irritation, as from a newgrowth affecting the cells of the second sensory stage, in the gray matter of the upper lumbar cord, may be sufficiently localized to produce a central pain projected to that part of the periphery under discussion. The susceptibility of the cells of the sensory chain is to be contrasted with the inexcitability of the tracts within the central nervous system, except the intramedullary portion of the posterior roots (Nicolesco). Espe-

cially could hematomyelia or syringomyelia give rise, for a time at least, to the clinical picture of meralgia paresthetica.

An unusual cause of meralgia was reported in one case by Roch and Mozer.[13] This patient developed herpes zoster, concurrently with the pustule of an ordinary smallpox vaccination; the vaccination had been given on the shoulder, and the herpetic eruption appeared on the opposite thigh in the region supplied by the external cutaneous nerve. Meralgia paresthetica persisted for months after the typical pains and eruption of zoster had disappeared. Clearly the immediate etiology of this meralgia was localized in the dorsal root ganglion.

Before dismissing the local for a consideration of constitutional influences affecting the sensory nerves in meralgia, one must take up the possible vascular complications from local conditions. Long and Mozer rule out intermittent claudication. Musser and Sailer also excluded it, finding too much additional symptomatology to fit into the meralgia complex: the affected leg during walking would become heavy, cyanotic, painful, and later paresthetic below as well as above the knee, with accompanying exaggerated reflexes and arteriosclerosis.

Lapinsky more recently suggests that the whole disease seems to be connected with some alteration in the blood circulation; he further states that while the paresthesias, dysesthesias, and skin sensory losses are centered in the lumbar segments, 1, 2, and 3, the centers for the same territory's bloodvessels lie in the lower thoracic segments. The lateral cutaneous nerve contains sympathetic fibers.

Pains due to affections of the vegetative nervous system—visceral sensation—probably give painful sensations in the extremities. Such affections may indeed play a part in cases of meralgia paresthetica. The ultimate destination of pain paths in the vegetative system is unknown (Nicolesco).

Various intoxications—as by alcohol (8 per cent according to Musser and Sailer), diabetes, lead, possibly gout—may cause the meralgic syndrome. A bilateral case in the course of diabetes has been reported by Kraus.[14] The conducting apparatus may here be changed by a lodging within the nerve or its sheath of autotoxic or heterotoxic substances so that a light external stimulus is interpreted as painful, or pain may be excited without an external stimulus (Behan).

Of the infections, typhoid fever and syphilis have been most often mentioned. Proximity of the nerve to the large intestine might facilitate the action of some infectious processes. In syphilis, a localized gummatous infitration has been suggested; cases are also on record in which the meralgic picture eventually transformed itself into that of the classical tabetic.

Pelvic inflammatory disease, acting locally on the nearby peripheral nerve is a sufficiently frequent cause of meralgia; pressure

and inflammation may both be operative under these circumstances. Lapinsky lays particular stress on the etiologic importance of inflammatory conditions in the pelvis and lower abdomen, going so far as to say that some disorders of the abdominal or pelvic organs *always* preceded meralgia in his series. He adds that an exacerbation of such a disorder was *always* followed by an exaggeration of the meralgia, and that treatment of the abdominal disease was *usually* followed by improvement of the meralgia. Intestinal inflammations, as enterocolitis or appendicitis, are rather uncommonly associated with meralgia, according to Long and Mozer. Lumboabdominal neuralgias, as reviewed for gynecologic conditions by Pavlovitch,[15] and various lumbosacral pictures may complicate or be complicated by the syndrome of meralgia paresthetica.

Pathologic changes of a neuritic character have been found in the peripheral nerve, but rarely. In cases with more centrally placed lesions alterations would be expected at corresponding levels, as for instance in cases where the syndrome was related to a tabetic process.

Treatment will necessarily vary with the particular etiology. Cases corresponding to those of Lapinsky, with pelvic and abdominal disease, or to those of Rosenheck with spondylitis, require surgical or other treatment primarily directed against the cause of the neural disturbance. The same may be said of central lesions, for example, the use of Roentgen rays in a hematomyelia. For symptomatic treatment, the measures commonly taken in cases of neuralgia and neuritis are notoriously inadequate. Removal of constrictions are, of course, indicated, as the adjustment of corsets, or the substitution of braces for a waist belt. A physiotherapeutic combination fairly effective in some cases seen by the writer, has been the following: radiant light and heat to the thigh and leg, followed by massage of the outer side of the thigh; blue pencil (static brush) discharge along the course of the external cutaneous nerve. More radical measures are Roentgen ray, alcohol injection into the sheath of the nerve (Long and Mozer), formalin injection as suggested by Foerster[16] and excision of the nerve as favored by Oppenheim in obstinate cases.

The histories of 2 cases, with different causation, follow:

Case Reports. CASE I.—K. H., a Russian Jewish furrier, aged forty years, was first seen by the writer four years ago, when his chief complaints were pains and paresthesias, numbness, tingling, burning and coldness, over the anterolateral surface of the left thigh; light pressure over the affected area caused marked burning, discomfort, and deep and superficial pain, while deeper pressure over a scar about 2 inches above the area caused similar though more intense symptoms, with a shooting and pinching pain extending to and most severe at a point just above the outer aspect of the knee.

The family history and personal history were negative. Syphilis was denied. Trauma took place during the man's military service, in October,

1918 (nine and a quarter years ago), when a rather superficial gunshot wound occurred at a point about 3 inches below the left anterior superior iliac spine. A small foreign body was removed through an incision 2 inches medial to the point of entrance.

The sense of numbness over the anterolateral surface of the thigh is said to have dated from the time of the wound, while the pains and burning sensations did not become troublesome until about a year later, when they came on gradually over a period of several months. The meralgic symptomatology remained stationary for about five years; in the past two years it has shown some net improvement subjectively, though objectively the same area is affected and the responses to stimuli are practically unchanged.

At present, almost the entire lateral aspect of the left thigh is affected, an oval area extending from just above the knee to a level slightly below the great trochanter and medially over the anterolateral surface of the thigh. The wound apparently lies distal to the division of the nerve, and the latter's gluteal branch is not involved. Other cutaneous nerve distributions are similarly free.

Subjective symptoms are of the same character now as they were three years ago, but milder in degree. Objectively there is hypesthesia to superficial touch, most marked at the extreme distal tip of the area involved; here the loss of sensation goes on to anesthesia after long standing. There is hyperalgesia to pain above, and hypalgesia below. The perception of heat is increased above, and normal below. The sense of cold is diminished over about the same area as is the sense of light touch. Possibly a little relative cyanosis can be detected at times. There are no trophic changes in the skin. The left calf is, however, $\frac{1}{4}$ inch smaller in maximum circumference than the right.

Complicating the condition four years ago were several large nodules in the right buttock which were said to have appeared after an injection (antitetanus?) about the time of the wound. Occasionally one would break down, healing rather slowly. The blood Wassermann had been negative, but when one of these nodules last flared up a year ago, the Wassermann became positive and an intensive course of antisyphilitic treatment (intravenous arsenical and intramuscular bismuth preparations) promptly caused their disappearance, leaving the pigmented areas now visible. This treatment had no apparent effect on the meralgia of the opposite thigh.

Central nervous syphilis has not been diagnosed. There is a little bilateral ptosis, and some diminution in hearing of the left ear. The deep reflexes and other neurologic signs are normal.

Osteoarthritis has not been apparent in the lumbar spine and is not shown by its Roentgen ray, although there have been suggestive pains and tenderness in the neck at times. Slight bilateral pes planus is present. Pains in the left heel are also complained of.

Hysteria (diagnosed in 1922) and neurasthenia (in 1923) indicate the persistent postbellum psychoneurosis, which has also complicated the picture in this case. The man has been a Government beneficiary since his discharge from military service and has done no work for years. The slight extent of improvement under physiotherapy, like the refusal of suggested operative interference, may have been somewhat influenced by considerations sometimes described under the head of "compensation neurosis."

CASE II.—J. H., a Danish physiotherapeutist, aged fifty years, was seen six months ago, when he complained of spontaneous pains, numbness, and particularly a sensation of freezing, over the anterolateral surface of the right thigh.

The family history was negative. In the personal history (lues and other infections being denied) there had been, twenty-five years ago, a single

attack of sciatic neuralgia in the same leg, lasting several weeks. Six or seven years ago, a sprain of the lumbosacral region following an accidental slipping while the subject was carrying a heavy patient. About three times yearly since this sprain he has a recurrence of severe lumbar pains and difficulty (on that account) in moving either leg, these symptoms lasting from an hour to a week. They are precipitated by some exceptional twist of the back, apparently involving more than usual rotation and lateral flexion.

Pains and paresthesias of the right thigh date back five or six years, that is, commencing rather gradually about a year after the sprain. They had been fairly constant up to six months ago, not varying with the attacks of lumbosacral pain just noted. Freezing was the most prominent of the paresthesias, but burning, tingling, and pains were felt at times, over the maximum unilateral meralgic distribution.

During the past thirteen years, for an hour or so daily, the subject has used a "control table" in his work, leaning upon it in such a way that its edge presses upon the right thigh just below the anterior superior spine of the ileum. This appears a more important factor in etiology than does the dorsal trauma, though the latter may indeed have played a part.

While numbness and coldness persist, pains have now disappeared following the use of the physiotherapeutic scheme already outlined, and an abdominal belt to correct a slightly pendulous abdomen.

The affected area covers the entire lateral aspect of the right thigh, extending to its midline in front, including half the patellar surface and reaching a line 2½ inches below its lower edge; above, the area reaches to within an inch of the anterior superior spine of the ilium, and extends above and behind the trochanter, that is, the nerve's gluteal branch is involved.

Objectively there is hypesthesia to superficial touch, and hyperalgesia to pain, over the entire area. Perception of heat is increased and that of cold decreased. There are no vasomotor, trophic, or motor changes.

Comparing this with Case I, there is no evidence of lues; none of flatfoot; and none of osteoarthritis of the spine at present. There is nothing psychoneurotic, and the subject never misses a day from work except when the occasional lumbosacral attacks of pain interfere.

Summary. The syndrome of meralgia paresthetica may result from sundry types of lesions that may be at the one time both irritative and partially destructive, acting on the peripheral nerve, on the dorsal root or its ganglion, or within the dorsal horn on the cell bodies of the sensory neurone of the second order.

The extent and exact location of the skin area affected varies markedly in different cases but is otherwise essentially similar. Many peculiarities are explainable by this fact, that besides peripheral anastomosing of the lateral cutaneous nerve with the anterior crural, genitocrural, and so forth, the former may itself arise from the first and third as well as the second lumbar root.

Failing effective treatment at the source, one may employ a suggested physiotherapeutic procedure, or surgical intervention.

One case is presented, showing the syndrome following a gunshot wound; a second case, following occupational trauma by a table-edge.

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A FLEXIBLE GASTROSCOPE.*

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Gastroscopy was first introduced by Trouve in 1873. It did not become an important diagnostic procedure, however, until Mickulicz devised his gastroscope in 1881. Since that time many types of gastroscopes have been constructed. They can essentially be divided into two groups: (1) The rigid apparatus and (2) the flexible type.

The important rigid gastroscopes are those of Mickulicz, Jackson,[4]

* We are deeply indebted to Mr. Jerome Lewine, a director of the Jewish Hospital of Brooklyn, for his kindness in defraying the expenses of this investigation.

This apparatus was constructed by Mr. R. H. Wappler, of the American Cystoscope Makers, Inc., Long Island City, N. Y.

Gottstein, William Hill, Elsner,[1] Schindler,[2] and Sternberg.[3] They represent the development of a rigid hollow tube, first with the use of the headlight, later a light carrier with the illuminating lamp passed through the tube into the stomach, and the latest types, a combination of illuminating and optical apparatus passed through the hollow rigid tube.

The flexible gastroscopes are those of Loening and Stieda, Kausch, Hoffmann, and Sussman. These instruments essentially consist of the distal third of the hollow tube made flexible by a silk woven material or a system of metal rings linked together. The whole apparatus is then straightened out by the introduction of another hollow rigid tube. There have been frequent objections raised to the flexible apparatus on the ground that one cannot see the structures lying directly ahead of the instrument when it is being introduced, thus introducing an element of danger of perforating the esophagus. It is claimed that when one introduces a rigid apparatus, one will not attempt to pass the instrument further when an obstruction or angulation is encountered in the esophagus. Our instrument obviates this danger, for when an obstruction is met which does not permit the passage of the flexible tube, the telescopic apparatus can be introduced with which the nature of the obstruction is determined.

Our apparatus embodies the following principles:

1. The introduction of a flexible armored cable with a soft rubber obturator.

2. The passage through the armored cable of a hollow rigid tube which contains an illuminating and telescopic apparatus.

3. The use of a water medium in the stomach for the transmission of images.

The apparatus consists of the following parts (see illustration):

1. A flexible wound steel tube, 56 cm. in length, 1.5 cm. in diameter.

2. A rubber obturator extending 6 cm. beyond the flexible metal tube.

3. A hollow rigid metal tube, 75 cm. in length and 1.2 cm. in diameter. This hollow tube has a blunt bevelled edge and contains a small tube through which the optical and telescopic apparatus passes. It is also equipped with an aperture for the introduction of tissue forceps.

4. Three telescopic systems, each one carrying its own lamp for proper illumination.

The first lens system to be used after the introduction of the flexible tube is the foroblique which was designed for Dr. McCarthy in the pan-endoscope. It carries the lamp on the distal end and is a continuation of the telescope without increasing the caliber in any place. An off-center lens is used in the objective which brings the inlet pupil close to the periphery and permits the light to enter

where the lamp is mounted opposite said inlet pupil. It is one of the most important achievements in endoscopy to look out through the end, and at the same time have the illuminator mounted on the end. As mentioned before, the objective has an off-center lens which means that a prism has been utilized to deflect the optical angle and a focus has been ground on to the hypothenuse of the prism. The prism has the effect of taking away almost all the light but this spherical surface restores the illumination.

Owing to the length of the telescope it has been necessary to insert at least 10 achromatic lenses, properly spaced apart in the telescopic tube in order to preserve the properties of the telescope. These consist of a large angle of vision, proper magnification at a given distance and enough brilliancy to recognize the object by ordinary illumination. The inner lumen of the telescope is only 4½ mm. in diameter. The entire length of the telescope is 90 cm. As far as the middle lenses and the ocular systems are concerned, the arrangement is the same in all three telescopes. In the right angle vision the objective lens system consists of a lens prism which reflects at right angles, and corresponding back lenses, two of which are used to straighten out this spherical aberration. Somewhat more complicated is the objective system of the retrograde vision where there are used a combination of an off-center lens and a hemispherical lens prism which are held in a setting so that the optical axis is first deflected about 25 degrees and then reflected about 120 degrees. In order to illuminate the field of vision properly a lamp is placed proximally and laterally to the inlet pupil.

This apparatus was designed for safety in introduction as well as for greater comfort to the patient. It is hoped that with the introduction of an apparatus with dangers considerably lessened there should result a more frequent application of this means for diagnostic and perhaps therapeutic purposes.

Procedure. *Preparation of Patient.* The patient should be fluoroscoped with a barium meal about twelve hours prior to the gastroscopic examination. The purpose of this is to determine the presence of angulations, sacculations and strictures of the esophagus.

The stomach should be empty at the time of gastroscopy, the patient having fasted for twelve to fourteen hours. Before introducing the gastroscope the stomach should be lavaged with warm tap water.

The usual procedure for anesthetizing the posterior wall of the pharynx is practised, swabbing with 15 per cent cocain hydrochlorid. A weak solution of novocain is also injected into the pyriform sinuses. In about ten minutes, when the glossopharyngeal reflex has disappeared, the patient is ready for the introduction of the apparatus.

Introduction of Gastroscope. The patient is seated on an adjustable table. The flexible tube with the obturator in place is intro-

duced in the same fashion as an ordinary stomach tube. The proximal end of the table is then lowered and the patient assumes a prone position with the head extended over the edge of the table. The obturator is then withdrawn. The hollow rigid tube with the foroblique telescope in place and the lamp lighted is then introduced. There are four points of narrowing and angulation of the

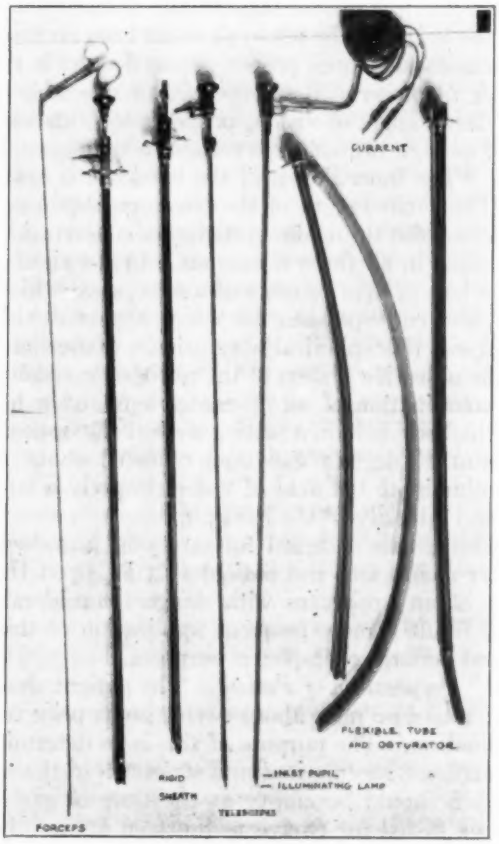

FIG. 1.—Gastroscope.

esophagus that the operator will meet with: (1) Level of cricoid cartilage (sixth cervical vertebra); (2) arch of aorta (fourth thoracic vertebra); (3) left bronchus (fifth thoracic vertebra); (4) diaphragm (tenth thoracic vertebra). When the operator approaches any of these points, he will experience some difficulty in passing the rigid tube. A slight refinement in technique, however, will result in passing the apparatus without any difficulty. When resistance to

passing the rigid tube occurs, one merely advances both the flexible and the rigid tubes, held firmly together, a distance of 2.5 cm.

After the apparatus has been passed into the stomach, warm tap water is permitted to flow in. We found in our experimental work, that a water medium for transmitting images was far superior to air.

Examination of the Stomach. With the foroblique telescope in place, rotating the whole apparatus 360 degrees in the same axis, gives one a field of vision on the greater curvature of the stomach well over 5 cm. in diameter. The greater curvature can be well inspected by slight changes in the axis.

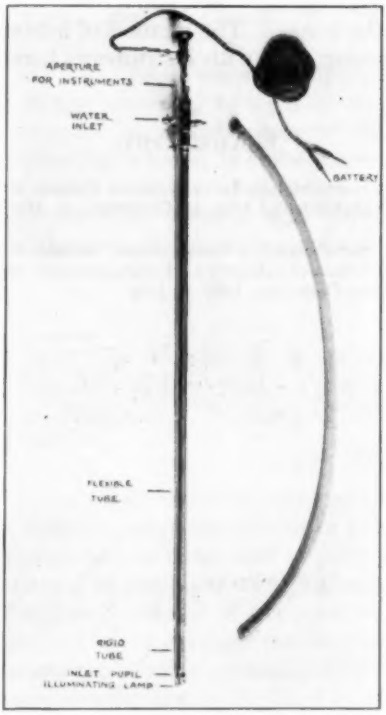

FIG. 2.—Gastroscope.

The advantage of the presence of the foroblique telescope in the rigid tube at the time of introduction is that it gives a forward vision and shows all the conditions under which the instrument is advanced so that the procedure is constantly under the guidance of the eye. Having assured oneself that the end of the tube has passed the cardia, and is lying close to the greater curvature of the stomach, the right-angle-vision telescope is then introduced. By moving the rigid tube in and out, and by rotating it about an

axis of 360 degrees, the walls of the stomach can be inspected. The final examination is then made with the retrograde telescope, with which there is clear visualization of the fundus of the stomach and the pylorus.

Care must be taken not to distend the stomach with too much water. About 300 cc. of water is sufficient for the gastroscopic examination, without distress to the patient. With some experience, one can learn to use the water irrigation as a focusing mechanism, for the flow of water will aid in keeping the mucous membrane away from the prism of the telescope.

Conclusions. A new type of flexible gastroscope has been described. Three telescopes are used and a water medium is employed for transmitting the image. The method of introduction is simpler and less discomforting than with instruments heretofore devised.

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3. Sternberg, W.: Sternbergschen Gastroskopie, Leipzig, C. W. Vogel, 1924.
4. Jackson, C.: Tracheobronchoscopy, Esophagoscopy and Gastroscopy, St. Louis, The Laryngoscope Company, 1907, p. 130.

REVIEWS.

TOBACCO AND PHYSICAL EFFICIENCY. A DIGEST OF CLINICAL DATA (WITH ANNOTATED BIBLIOGRAPHY). By PIERRE SCHRUMPF-PIERRON, M.D., Professor of Clinical Medicine, University of Cairo. Pp. 126. New York: Paul B. Hoeber, Inc., 1927. Price, $1.85.

THIS is a brief (fifty-five page) résumé of laboratory and clinical evidence bearing on the action of tobacco on the body functions, with particular reference to the detrimental effects of excessive smoking. Of outstanding interest is the apparent causal relation of smoking with nervous disorders ranging from vertigo and headache to psychosis, amnesia, aphasia and peripheral and optic neuritis. The bibliography is complete and the text is not controversial. C. S.

DISEASES OF THE SKIN. By ROBERT W. MACKENNA, Lecturer on Dermatology, University of Liverpool. Pp. 452; 36 color plates; 143 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, $7.50.

THIS is really an excellent textbook of moderate size, adapted to the use of the average practitioner both in this country and in Europe. The sections on anatomy and physiology are well condensed. The technique of examination and treatment is relatively simple and easily within the range of the practising physician. A genuine effort is made to follow etiologic rather than the old morphologic classifications and the effect in general is distinctly illuminating. The amount of space and illustration devoted to tuberculosis of the skin, and particularly to lupus vulgaris, is out of proportion to its relatively lesser importance in American practice. Of the more modern forms of therapy, the quartz lamp is tersely but satisfactorily discussed. Roentgen ray treatment is given in terms of the Pastile dosage system, now entirely superseded in this country by the MacKee technique, and hence unintelligible in American practice. The causation of eczema and eczematoid dermatitis is discussed under predisposing and exciting heads, but space limitations probably prevent as complete a discussion as would seem desirable. The familial and hereditary background of psoriasis is strongly emphasized.

The consideration of syphilis is of necessity very brief, but important differential points in the cutaneous manifestations are well emphasized. There is practically no discussion of visceral manifestations. Therapy is likewise very brief and confined largely to neoarsphenamin and mercury.

This book bears the stamp of the good qualities of an individual and personal presentation in the form of clear-cut didactic statement. The photography is excellent and some of the illustrations really superb. Even the colored plates are better than usual. There is still a tendency to the selection of exhibition photographs, a fundamental mistake, the reviewer believes, in textbook pedagogy. On the whole, the book sets a standard which American texts can well afford to notice. J. S.

MEDICINE MONOGRAPHS. VOL. XIII. HYPOTENSION. By ALFRED FRIEDLÄNDER, Professor of Medicine, College of Medicine, University of Cincinnati. Pp. 193. Baltimore: Williams & Wilkins Company, 1927. Price, $2.50.

THIS monograph, said to be the first critical and analytical study of the literature of low blood pressure, is a very valuable and complete study. Temporary hypotension and that due to mechanical causes, as well as that associated with constitutional diatheses and acute and chronic disease, are discussed in detail. The hypotension produced by certain tissue extracts and certain drugs also comes in for a fair share of discussion. But the types of low blood pressure related to endocrine disorders and to malfunction of the factors that normally influence blood pressure seem to claim the author's greatest interest. He emphasizes, also, the facts that no adequate explanation has yet been found for certain types of hypotension and that low blood pressure is in many instances compatible with perfect health. The book closes with an excellent bibliography.

K. A.

TONIC HARDENING OF THE COLON. By T. STACEY WILSON, M.D., B.Sc., F.R.C.P. Pp. 210. London: Oxford University Press, American Branch, 1927.

NEW points of view in medicine are always fascinating, even though at first they appear fantastic. We have of late become accustomed to radical changes in our conceptions of disease as the result of laboratory discoveries, but the author here presents almost entirely as an outgrowth of his long clinical experience, a conception of tonic fixation of the colon (not necessarily contraction), which he believes explains many varied complaints, ranging from abdominal

pains to severe mental aberrations. Many will question his hypothesis, but he refers to work of Sir Charles Sherrington which seems to support his ideas and gives many personal case reports, covering a period of forty years, that at least justify serious consideration.

T. M.

HÄMATOLOGISCHES PRAKTIKUM. By H. ZIEMANN, Professor, University of Berlin. Pp. 166; 37 illustrations. Berlin: S. Karger, 1927. Price, geb. Mk. 7.20.

IN one hundred and sixty-six pages the author has succeeded in giving a satisfactory review of hematology. The most valuable feature of the book are tables of differential diagnosis, one of hemophilia, scurvy and the purpuras, another of the leukemias and allied conditions. Unfortunately, the author has given space to inadequate discussions of the treatment of the various diseases. These seem a little out of place in such a book. On the whole, the book differs but little from other similar handbooks. The illustrations are few and not particularly good.

O. P.

MODERN ASPECTS OF THE DIAGNOSIS, CLASSIFICATION AND TREATMENT OF TUBERCULOSIS. By J. ARTHUR MYERS, Associate Professor of Preventive Medicine, Medical and Graduate Schools, University of Minnesota. Pp. 268; 27 half tones; 7 line cuts; bibliography index. Baltimore: The Williams & Wilkins Company, 1927. Price, $5.50.

IN this "handbook for students and practitioners" the author "has endeavored to gather together facts concerning the tubercle bacillus, and the diagnosis, treatment, prognosis and prevention of tuberculosis, which may be quickly grasped and applied, alike by the student and the practitioner of medicine." The chapters on diagnosis and on treatment, though brief and incomplete, better attain their objective than those on pathogenesis and prevention. The former contain excellent quotations from Stewart, Amberson and Krause, which, however, lose somewhat from dissociation from their context. The importance of the presence of the tubercle bacillus in sputum is recognized in diagnosis, but not given due emphasis in relation to the prevention of massive infection of those living in the same household. There is no reference to the importance of examination of contacts of sputum-positive cases, in order to detect diffuse pulmonary infiltrations in their latent or preclinical stage.

The author appears (page 62) to give as great weight to the

appearance of a positive tuberculin test in an adolescent as in an infant.

In the discussion of apical tuberculosis much is made of changes in the roentgenographic appearance of the hilum shadow, which are ascribed to lesions within the hilum. The author does not envisage the possibility that such changes in appearance may be due to projection onto the single plane of the film of shadows of densities situated anterior or posterior to the hilum.

The artificial pneumothorax operation is mentioned but not described, although it is surely of importance in the care of patients discharged from sanitarium.

On the whole, the book gives an impression of hurried writing. Successfully to achieve its purpose within the compass of two hundred and sixty-eight pages would require greater care and more succinct presentation. F. McP.

PERNICIOUS ANEMIA. By BEAUMONT S. CORNELL, M.D., Fellow of Duke University. Pp. 311; 7 illustrations. Durham, N. C.: Duke University Press, 1927. Price, $4.00.

OF the several books that have recently appeared on pernicious anemia, this seems the most useful. Not only has it the advantage of including the Minot-Murphy "liver" therapy and the most recent researches on the nature of the disease and its etiology, but the historical aspects are adequately considered both as the subject matter of Chapter II and in the treatment of the various phases of the subject. Medical men will perhaps be mildly surprised at the first ten pages "for nonmedical readers," but cannot help being delighted with the bibliography of 827 references. The modest and painstaking presentation of the critical review of the literature inspires unusual confidence in its accuracy, and in no subject is the need for accuracy greater than in this.

Duke University is to be congratulated on this early offspring of its press. E. K.

THE MEASUREMENT OF MENTAL CAPACITIES. By CYRIL BURT, M.A., D.Sc., Professor of Education in the University of London and Psychologist to the Education Department of the London County Council. Pp. 52; 14 illustrations. Edinburgh: Oliver & Boyd, 1927. Price, sixpence.

THIS author says though mental science has not made the forward stride of physical science, at last it is well under way, and he feels that before the present century is over mental science shall have been found to greatly influence civilized life.

A "psychometric scheme" is offered in which the mental characteristics are divided into: (1) Intellectual: (*a*) Inborn capacities; (*b*) acquired attainments. (2) Temperamental: (*a*) Inborn tendencies; (*b*) acquired tendencies.

Further subdivision is then given to this interesting—and possibly useful—classification. N. Y.

UROGRAPHY. By WILLIAM F. BRAASCH, M.D., Head of Section of Urology, Mayo Clinic; Professor of Urology, Graduate School of Medicine, University of Minnesota. Second edition, revised and enlarged. Pp. 480; 759 roentgenograms. Philadelphia and London: W. B. Saunders Company, 1927. Price, $13.00.

TWELVE years having elapsed since the first edition of this work, its rebirth is welcomed for *Urography* has grown apace. The premier edition stood alone in its day, and the present volume brings to the reader the immense experience of twelve more years of active work at the Mayo Clinic. Chapters have been added on cystography and urethrography, the number of illustrations doubled, the text rewritten and greatly increased and the modern technique clearly described. The general surgeon and the internist will be interested in the scope of diagnostic possibilities; to the urologist and the roentgenologist the book is indispensable. A. R.

ORGANIC INHERITANCE IN MAN. By F. A. E. CREW, Director of Research in Animal Breeding at the University of Edinburgh. Pp. 214; 37 illustrations. Edinburgh: Oliver and Boyd, 1927. Price, 12s., 6d. net.

WRITTEN for the general practitioner, this book aims to present the recent advances in the science of genetics. Since the author has made no attempt to confine his diction to words of one syllable, the reader will find it a little more condensed than some of the recent popular works in the same field. Describing the two laws of Mendel, the author discusses briefly but adequately the theory of the gene, sex determination and the effects of inbreeding. One half the book, however, is devoted to inheritance in man, listing some 219 physical and pathologic characters that seem to be inherited. In the chapters on human inheritance the author treats of resistance to disease, and expresses in conclusion his very sane opinion of eugenics. On the whole the book presents an authoritative summary of the recent advances in genetics, particularly as applied to man. H. C.

BOOKS RECEIVED.

New Books.

Einführung in die Mechanik des Kreislaufes: Handbuch der biologischen Arbeitsmethoden. By GEN. MED. RAT. PROF. DR. EMIL ABDERHALDEN. Abt. V. Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Orgnismus, Teil 8, Heft 1. Pp. 236; 106 illustrations. Berlin and Wien: Urban and Schwarzenberg, 1928. Price, Mk. 13. The 255th item of a series still far from finished. This number is chiefly of value to experimental physiologists and pathologists.

*Anthelmintics and Their Uses.** By R. M. CHOPRA and ASA C. CHANDLER. Pp. 291; 5 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $5.00.

Guy's Hospital Reports, January, 1928. Volume 78 (Volume 8, Fourth Series), No. 1. Edited by ARTHUR F. HURST. Pp. 126; illustrated. London: The Lancet, Ltd., 1928.

*A Treatise on Diseases of the Hair and Scalp.** By S. DANA HUBBARD, M.D. Pp. 500; 81 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $5.50.

Health Record for Women. By J. THERON HUNTER, M.D. Pp. 64. Baltimore: Williams & Wilkins Company, 1928. Price, $1.00. "To encourage women to keep complete records of their state of health" 23 charts with explanations have been published in book form. A sequel to the author's *Health Record for Children.*

*Hormone and Innere Sekretion.** By DR. FRITZ LAQUER. Pp. 136. Leipzig: Theodore Steinkopff, 1928.

*Handbook on Diet.** By EUGENE E. MARCOVICI, M.D. Pp. 323. Philadelphia: F. A. Davis Company, 1928. Price, $3.50.

*The Simple Goitre.** By ROBERT MCCARRISON, C.I.E., M.D., D.Sc., LL.D. Pp. 106; 143 illustrations. New York: Wm. Wood & Co., 1928. Price, $4.00.

Medical Department of the U. S. Army in the World War: IX. Communicable and Other Diseases. Pp. 628. Washington: U. S. Government Printing Office, 1928.

*Safeguarded Thyroidectomy and Thyroid Surgery.** By CHARLES CONRAD MILLER, M.D. Pp. 261; 52 illustrations. Philadelphia: F. A. Davis Company, 1928. Price, $3.75.

*What You Should Know About Heart Disease.** By HAROLD E. B. PARDEE, M.D. Pp. 120; 1 illustration. Philadelphia: Lea & Febiger, 1928. Price, $1.50.

*Treffe Ovarienne and Action Endocrine de l'Ovaire.** By VITTORIO PETTINARI. Pp. 487; 181 illustrations. Paris: Gaston Doin & Cie, 1928. Price, 70 fr.

*Cardiac Arrhythmias.** By IRVING R. ROTH, M.D. Pp. 210; 80 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $7.50.

Schizophrenia (Dementia Precox). Vol. V. Association for Research in Nervous and Mental Disease. Pp. 491; 61 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $7.50.

Acute Aplastic Anemia: Its Relation to a Liver Hormone. By A. Hayes Smith. Pp. 80. London: H. K. Lewis & Co., Ltd., 1928. Price, 6/. On the basis of a case of aplastic anemia that became polycythemic after liver feeding, a theory of the hormonic action of the liver in the hemopoietic function of the bone marrow is presented.

Transactions of the American Surgical Association. Vol. 45. Edited by John H. Jopson, M.D. Pp. 516; illustrated. 1928.

The Medical Department of the United States Army in the World War. XIII. Part I. Physical Reconstruction and Vocational Education. Part II. The Army Nurse Corps. Pp. 998; 13 illustrations. Washington: The U. S. Government Printing Office, 1928.

*Traité d'Electrocardiographie Clinique.** By Paul Veil and Juan Codina-Altes. Pp. 448; 197 illustrations. Paris: Gaston Doin & Cie, 1927. Price, 95 fr.

New Editions.

A Manual of Otology. By Gorham Bacon, A.B., M.D., F.A.C.S., and Truman L. Saunders, A.B., M.D., F.A.C.S. Eighth edition. Pp. 576; 194 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $4.50. The authors preface that this is a thorough revision with addition of new matter and illustrations, and omissions of obsolete remedies and methods.

Practice of Medicine. By Hughes Dayton, M.D. Fifth edition. Pp. 340. Philadelphia: Lea & Febiger, 1928. Price, $2.25. The parts on scarlet fever, goiter, diabetes and Bright's disease have been revised and the commoner affections of the upper respiratory and digestive tracts included.

The Use of Symptoms in the Diagnosis of Disease. By Hobart Amory Hare, B.Sc., M.D., LL.D. Ninth edition. Pp. 528; 128 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $5.50. An aid to the young physician who "has been taught how to make a diagnosis in the laboratory but not at the bedside."

Clinical Aspects of the Electrocardiogram. By Harold E. B. Pardee, M.D. Second edition. Pp. 242; 60 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $5.50. A good book brought up to date on the electrocardiographic advances of the past four years. References, index and some of the subject matter could be somewhat expanded to even greater advantage.

*Atlas of Human Anatomy.** By Johannes Sobotta. Edited from the sixth German edition by J. Playfair McMurrich. Second English edition from sixth German. Pp. 785; 338 illustrations. New York: G. E. Stechert & Co., 1927. Price, $15.00.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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A Record of Fifty Consecutive Cases of Pregnancy and Parturition in Patients with Crippled Hearts.—There has always been considerable discussion as to the handling of women with organic heart disease who become pregnant. A considerable number of papers have been written on this subject, but the present one by HAY and HUNT (*Lancet*, 1928, i, 271) seems worth a special study because they give in more or less detail the results of 50 carefully followed cases of heart disease in patients who became pregnant. As this paper is such an excellent one, and because of the authority that the senior author has, it might be well to quote in detail some of the paragraphs of this paper:

"Pregnant women with diseased hearts must be treated primarily as cardiac patients, and the first indications of cardiac failure noted. They must be under regular medical supervision throughout. Among the poor an antenatal clinic and a rest home are of the very greatest value. In every patient the reserve power of the heart must be increased by adequate rest and symptomatic treatment. Rest is essential, more especially in the four to six weeks before labor. Dyspepsia, flatulency, constipation, insomnia, bronchitis and other discomforts must be remedied. If there is auricular fibrillation it must be controlled with digitalis and the optimum dose found and maintained. Any woman with auricular fibrillation must be kept under constant supervision.

"During labor the aim is to lessen the nervous and physical exhaustion of the first stage and to diminish the physical strain of the second stage. Light anesthesia during the second stage is helpful, and narcotics are valuable; they reduce the voluntary effort. An early resort to instrumental help is most important.

"In the earlier months cardiac failure which refuses to respond to treatment justifies immediate intervention, especially if there be persistent retching and vomiting. At times there is a peculiar and unexplained cardiac failure in earlier months—certainly not due to mechanical causes—which resists treatment and is only relieved by terminating

the pregnancy. Induction, however, should never be attempted until compensation has been restored as far as possible by rest and drugs. The stress of labor is likely to prove fatal to a woman whose heart is already struggling with difficulty to maintain the circulation.

"Experience has shown that the majority of women with crippled hearts, in whom the cardiac reserve is good, are capable of pregnancy and labor without any great additional risk. This is especially true if the cardiac lesion is not progressive and if there is no history of a previous cardiac breakdown. There is admittedly an increased risk, but it is one that many women are prepared to take and which is not unreasonable under constant supervision. In multiparæ a knowledge of the manner in which the previous pregnancy was tolerated is an excellent guide.

"The mere presence of mitral stenosis or even aortic regurgitation, the occurrence of premature beats, the existence of cardiac pain and tenderness over the cardiac thrust, and the presence of cardiorespiratory bruits, do not in themselves justify a childless marriage. So long as the cardiac reserve is good, so long as the response to effort is satisfactory and there is no undue enlargement of the heart, the presence of valvular disease is no bar either to marriage or pregnancy. When, however, there is a clear history of cardiac failure and distress during a previous pregnancy, and if it is known that after labor convalescence was unduly prolonged, owing to cardiac weakness, then a definite veto must be given. Such a decision is all the more imperative if the cardiac distress had increased as pregnancy progressed and become urgent and alarming during the act of parturition.

"The same opinion is justifiable in cases with auricular fibrillation; advanced mitral stenosis, as shown by a large heart, a long diastolic bruit and a small cardiac reserve; advanced aortic regurgitation with a big heart, Corrigan's pulse and defective reserve.

"It is the borderland cases that present the greatest difficulty. In them any abnormality in the pelvis likely to prolong labor becomes a very great importance.

"A pregnancy woman who is aware of her cardiac disability should be reassured. Too often the risks are unduly stressed, and her pregnancy is overclouded by fear and apprehension—an apprehension frequently aggravated and intensified by a fussy spouse. The necessity for careful supervision must be emphasized, and the importance of rest and sensible behavior discussed with her quite freely. Motherhood is woman's peculiar privilege and prerogative, a privilege which we have no right to refuse her without adequate reason.

"Pregnancy inevitably entails certain risks, which a woman accepts in order that she may have a child. A crippled heart is an added risk, and it may be an unjustifiable risk. But the more I have studied these patients the more I have been impressed with the wonderful manner in which their hearts have responded to care and treatment during pregnancy. I believe that a woman with valvular disease is entitled to know to what extent the normal dangers of pregnancy are increased by her cardiac lesion, and if she is prepared to face the ordeal, then we must do all we can (and we can do a very great deal) to minimize the dangers of pregnancy and parturition by constant supervision and prompt and efficient treatment—both medical and surgical."

SURGERY

UNDER THE CHARGE OF

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Diaphragmatic Hernia. TRUESDALE (*J. Am. Med. Assn.*, 1927, **89**, 2248) says that diaphragmatic hernia is one of the concealed deformities, exceedingly difficult to diagnose, unless the examiner has it in mind. The problems associated with diaphragmatic hernia present a fascinating study. The condition produces altered function of the heart and lungs. It affects the stomach, liver, intestines, kidneys and pancreas, because at one time or another all these structures have been observed above the diaphragm. Why does not the patient die who has a diaphragmatic hernia from external violence? There is always pressure of considerable degree against the mediastinum. It is this factor—the mediastinum in man is not a swinging structure. It moves within a narrow range. On the other hand, in the infant the mediastinum is pushed way over to the side and the child frequently dies. So it is with experiments on some of the lower animals. In diaphragmatic herniæ the air in the hollow viscera first produces stasis, then, as it increases, incarceration, and finally obstruction. Obstruction, but not strangulation, is produced, because the ring in the diaphragm is not dense and fibrous, as is the umbilical ring or the inguinal ring. In the diaphragm there is enough elasticity to the margin of the ring to permit the circulation to continue in spite of the fact that the lumen of the intestine is constricted, so as not to permit the passage of intestinal contents. Therefore strangulation almost never occurs in diaphragmatic hernia. Consequently there is seldom great emergency even about obstruction in diaphragmatic hernia. If the colon is involved in the hernia a laparotomy should not be done to cure the hernia. The first step to be taken is an appendicostomy or a cecostomy. This will relieve obstruction, provide a safety valve and thus lower the mortality from more than 50 to 5 per cent. This is brought about by doing the operation at a later period, when the patient is in a satisfactory condition.

Tularemia.—MERRIMAN (*Minnesota Med.*, 1927, **10**, 719) states that tularemia is primarily an acute infectious disease of rodents and wild rabbits and secondarily a disease of man—a new disease discovered by Americans—one of the few infections transmitted from the lower animals to man, directly or indirectly, through the medium of parasites. It is a disease appearing in four distinct and characteristic forms with a morbidity and mortality toll as serious as that of typhoid fever, resistant to all present forms of therapy and occurring in an alarming and increasing frequency in all parts of the country. The onset is

sudden, with severe headache, chills, fever, nausea, vomiting, general pains, sweating and prostration. There are four clinical forms: The ulceroglandular type, in which there is pain, tenderness and slight enlargement of the lymph glands draining the portal of entry; the oculoglandular, where the portal of entry is the conjunctival sac; the glandular type—identical with the first form except that there is no ulcer; in the fourth type, the typhoidal, fever is the only outstanding symptom for there are no glandular or localized symptoms.

Prostatic Calculi.—THOMAS and ROBERTS (*J. Urol.*, 1927, **18**, 470) say that prostatic calculi have ceased to be a clinical rarity and are of much commoner occurrence than the number of cases reported. The etiology of true prostatic calculi is still hypothetical. True calculi, whether septic or aseptic, have as a nucleus the corpora amylacea, which are albuminoid or nitrogenous-like bodies. These prostatic calculi are usually multiple and millet seed to pea size. They are commonest in middle and late life and associated with other pathologic conditions. About 65 per cent are symptomless and are found accidentally during routine Roentgen ray or at operations on the prostate. A persistent and rebellious prostate should arouse suspicions of calculi. Serious sequelæ are rare, such as abscess or gangrene. Diagnosis from malignancy and inflammatory nodules can be made in almost 100 per cent of cases by means of roentgenograms. Phleboliths must be taken into consideration. Surgical intervention by the perineal route is the treatment of choice, except in those cases where the calculus communicates with the urethra when it may be removed urethroscopically.

Local Anesthesia in Thyroidectomy.—WALTHER (*Kentucky Med. J.*, 1927, **25**, 141) claims that operations for goiter were among the earliest surgical procedures, wherein general anesthesia was replaced by local anesthesia. It greatly reduces the risk of injury to the recurrent laryngeal nerves, avoids the liability to bronchitis and postoperative pneumonia and almost entirely does away with vomiting after operation, which is very dangerous, annoying and predisposes to hemorrhage. There is a special advantage in local anesthesia in cases of toxic goiters, for the reason that the heart in these cases most often has been damaged to an extent to make any general anesthetic a greater risk and in some of the worst cases general anesthesia is absolutely contraindicated. Local anesthesia has been employed by three methods, namely (*a*) terminal infiltration, (*b*) field block and (*c*) nerve block. Nerve block regional anesthesia has become the most popular and is the most satisfactory. Cervical plexus block is accomplished by two methods: (1) Injection of the nerve trunks at the level of the point of exit of the cutaneous nerves, a point corresponding to the middle of the posterior border of the sternomastoid muscles; (2) the injection of the point of junction of the second, third and fourth cervical roots at the level of their exit from the intervertebral foramina in front of the transverse processes. The next injection is at the upper poles, along the region of the superior thyroid arteries. The last injection is along the line of the collar incision of Kocher, which should encircle the anterior lower part of the neck just above the sternum.

THERAPEUTICS

UNDER THE CHARGE OF

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The Use of Insulin to Improve Nutrition in Nondiabetic Patients.—WIECHMANN (*München. med. Wchnschr.*, 1927, **74**, 2207) reports most favorable results from the administration of small but gradually increasing doses of insulin for the purpose of increasing the weight of undernourished adults, thus confirming the experience of Falta, Vogt and others. He finds that this form of treatment is especially indicated in cases of constitutional undernutrition and in patients suffering from visceroptosis. The well-known antagonism between insulin and thyroxin also renders the former valuable for use in the undernourished thyrotoxic patient. Further it has proved of value in building up afebrile or subfebrile tuberculous patients, although it must be used with great care on this group in order to avoid possible activation of the tuberculous process. The increase of weight produced by insulin, while progressive, is strictly limited, and it is unusual for patients to gain more than enough to restore them to the average normal for their height and build. Ambulatory cases are started with two doses daily of 5 units each. Then for about fourteen days 10 units are given twice daily, this being gradually raised to 20 units twice and, finally, to 20 units three times per day. Doses for patients in bed may be increased sometimes to as much as five daily injections of 30 units each. In general, the injections should be given a half hour before meals and the last injection should not be given later than 7 P.M., in order to avoid the danger of the development of hypoglycemia during the night. No special modifications of the diet are necessary except that at least 50 gm. of carbohydrate should be provided at each meal. Under this plan of treatment there seems to be virtually no danger of inducing marked insulin hypoglycemia. Aside from the gain in weight and the improved general state of the nutrition, it is noteworthy that the size of the heart is somewhat increased in these patients under the influence of insulin. This seems to be due chiefly to increase in the total blood volume. Metabolic tests show that the use of insulin increases the transformation of carbohydrates into fats. There is a marked increase in the patient's appetite which seems to be related to the demonstrated fact that insulin shortens the emptying time of the stomach.

Increase in the Milk Flow of Nursing Mothers through Heliotherapy.—STOLTE and WIENER (*Deutsch. med. Wchnschr.*, 1928, **54**, 259) review the unsatisfactory results obtained by all of the usual methods employed for increasing milk production in the human breasts. On a basis of many years of experience they have found that skillful emptying of the breasts by prolonged gentle massage, carried out from two to five times

a day, has been the only satisfactory measure available. The procedure is somewhat painful even in the most skilled hands, and in unskilled hands is too painful for ordinary employment. It is very time consuming. Accidentally, while treating a case of mastitis by massaging the breasts and the local application of radiation from the quartz lamp, the authors observed an enormous and very rapid increase in the patient's milk production. Following up this accidental observation they employed local heliotherapy in a series of twenty unselected patients in whom the milk supply was failing or had already failed. The study was carried out under careful control, and other methods of treatment had been employed in some of the patients without benefit. The use of heliotherapy in every patient produced a marked increase in the flow of milk so that the waning supply became abundantly adequate to nourish the baby. In one patient the total quantity of milk before treatment which could be obtained after an eight-hour rest of the breasts amounted to 55 gm. At the end of fourteen days of heliotherapy this had risen to 700 gm. per day, and it continued to rise until the baby was obtaining from 1000 to 1200 gm. They expose the breasts daily to a quartz lamp, beginning with periods of from five to seven minutes and increasing gradually to an exposure lasting from twenty-five to forty-five minutes. Particular care is taken to avoid burning of the skin, while the effort is also made to give a sufficient dose to produce a definite though slight skin reaction. It is often necessary to protect the nipple by the application of vaseline. So striking have been the results in this small series of controlled cases that the authors report them now in the hope that others will take up the investigation in order to determine whether or not it is of definite value.

PEDIATRICS

UNDER THE CHARGE OF

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The Prevention and Modification of Measles by Measles Antidiplococcus Goat Serum.—HALPERN (*J. Am. Med. Assn.*, 1928, **90**, 1109) gave 50 patients in whom there was a definite history of never having had measles, measles antidiplococcus goat serum as a protection against measles. Five of these patients died in from three to ten days after receiving the serum, but their deaths were due to the illness for which they were originally admitted to the hospital. They did not develop measles nor was there any serum sickness before their deaths. Of the remaining 45 patients, 28, or 63 per cent, were successfully protected. Although 17 developed the disease, the majority of these showed an attenuated form of the illness. Eight patients received serum after four days from exposure. Of these, 3, or 38 per cent, were protected. Another noteworthy observation was that not a single

complication occurred in any of the patients treated with the serum who developed the disease, nor was there any instance of a serum reaction in the entire series. The measles antidiplococcus goat serum is both antibacterial and antitoxic and the author states that it can be produced in sufficient quantities to meet all necessary demands.

The Roentgen-ray Diagnosis of Infantile Scurvy.—BROMER (*Am. J. Roentg. and Rad. Therap.*, 1928, **19**, 112) states that the diagnosis of scurvy on the roentgenogram in its well-developed stages is not difficult. This is contrary to the belief of many and the statements in the text-books. The disease shows four roentgenographic stages. The first is the most important because it is possible to diagnose the early stage of the disease on the roentgenogram while the clinical diagnosis is still uncertain. The fourth, or healing, stage may show characteristic signs, even though, as in some of his cases, five years have passed since the onset of the disease. The terms of the present nomenclature, such as white line, scurvy line, trümmerfeldzone, the author thinks are very confusing; he prefers such terms as, broadened zone of preparatory calcification and framework marrow zone, which typify the histologic changes that take place in the course of the disease and when applied to the roentgenographic changes do not permit any confusion.

The Pirquet Test: Comparison of the Scarification and the Puncture Methods of Application.—STUART (*Am. J. Dis. Child.*, 1928, **35**, 388) reports that the effective method of applying the Pirquet test is to make a single puncture with an ordinary sewing needle and to penetrate the epithelium through a drop of tuberculin. The advantages of this method are, that it may be performed rapidly and is less objectionable to the child than the scarification technique usually employed. Another advantage is that there is no need of supervising the child until the tuberculin dries on the skin for, after puncturing the epithelium through the drop of tuberculin, the excess tuberculin may be wiped off immediately without altering the effect of the test to any great extent. Using this method the author obtained 100 per cent positive reaction in 223 children who had positive reactions with the scarification method. He found that when such a needle was used in making the puncture through two separate drops of tuberculin placed on the forearm the second site of puncture often produced the most pronounced reaction. In the 223 cases the drop of tuberculin was removed immediately after the puncture and notwithstanding, the positive reaction was obtained in all the cases. When the test was performed without applying a drop of tuberculin to the skin, but the only tuberculin introduced being that adhering to the tip of the needle having been passed through a drop of tuberculin placed on a different area, the reactions were usually, but not always, positive in persons sensitive to tuberculin.

The Effect of Parathyroid Extract on Mineral Metabolism in Infantile Tetany.—SHOHL, WICKMAN and SHORR (*Am. J. Dis. Child.*, 1928, **35**, 392) present the results of administering small amounts of parathyroid extract in 2 cases in infantile tetany. On 1 infant the drug had little effect; in the other case there was a control of the symptoms and an improvement, as shown by clinical and chemical manifestations. This

improvement was transitory and disappeared when treatment was stopped. The alterations were brought about without gross changes in the calcium and phosphorous metabolism. A normal secretion of sodium and potassium was observed during the period of administration of parathyroid extract with relief of symptoms. During the relapse that followed the withdrawal of parathyroid therapy the excretion of sodium increased and potassium was retained in the body.

The Hearts of Normal Children.—Lincoln (*Am. J. Dis. Child.*, 1928, **35**, 398) presents the observations made on a large number of children. She found that the girls from four to twelve years of age had a more rapid horizontal heart rate than boys of the same age, while the vertical pulse rate is equal in boys and girls except at eleven and twelve years of age, at which time the heart rate of the girls is higher than that of the boys. She was unable to demonstrate any significant difference as regards sex in the blood pressure in children of three to thirteen years of age and the pulse pressure did not vary greatly with sex and only slightly with age. In contrast to the electrocardiographic studies on the same children the regularities of the heart decrease with age in children from two to thirteen years. Transient systolic murmurs of the cases were not of demonstrable significance in this group of normal school children. Symptoms referable to the circulatory system were present only in those showing marked deviation from the normal heart size or in those showing the "effort syndrome."

Nontuberculous Fibrosis of the Lung in Children.—Agassiz and Gill (*Arch. Dis. Child.*, London, 1928, **3**, 1) have found nontuberculous fibrosis of the lung to be a very common disease in children. They believe that it is often overlooked or else diagnosed as pulmonary tuberculosis. They found a high incidence of measles, whooping cough and pneumonia in the previous history of their cases. Scarlet fever, diphtheria, chickenpox, rubella, mumps and influenza occurred in a few cases and empyema was noted in one case. The occurrence of these diseases had little bearing on the origin of the fibrosis. Pneumonia was often found in the history. The treatment of this condition is mainly palliative. The ordinary open-air treatment in convalescent homes or sanatoriums for children is very satisfactory. Prevention of the onset of catarrhal conditions should be practised as much as possible. They recommend creosote in increasing doses upon the onset of any fetor of the breath, and they have found that very young children will take up to half a teaspoonful without complaining.

Borderline Problems in Pediatrics and Urology.—Kretschmer (*Atlantic Med. J.*, 1928, **31**, 452) stresses the resemblance of the urologic problems in infancy and early childhood to similar problems in adults. He feels that the technique of urologic examination and medication can be mastered with practice and when the operator has become skilled in the smaller instruments no difficulties will arise. He strongly urges early, careful and complete urologic examination and study in all cases that do not promptly respond to treatment. Instrumental therapy, such as lavage and pyelitis and litholapaxy in the treatment of stones in the bladder should be accomplished with the same precision in childhood as in adults.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Tumors of the Internal Organs in Mycosis Fungoides.—LIECHTI (*Arch. f. Derm. u. Syph.*, 1928, **154**, 246). **The Nature of the "Metastases" in Mycosis Fungoides.**—EICHLER and ROTTMANN (*Arch. f. Derm. u. Syph.*, 1928, **154**, 300). These two articles reflect the controversies now in progress as to the malignant *versus* the granulomatous character of lymphoma-like diseases of the skin, including mycosis fungoides, the leukemias and leukosarcomas and Hodgkin's disease with cutaneous manifestations. The former author insists, on the basis of the histologic picture as studied in the smallest and earliest lesions, that the process is at bottom granulomatous, and that the large-celled infiltrations, with many mitoses, the destructive growth and infiltration and perforation of the walls of bloodvessels are merely expressions of a late facultative assumption of malignant characteristics. The latter authors deny the malignant concept, espoused chiefly by Ewing and Fraser in this country, even this amount of probability. They maintain that there is no evidence that the original infiltrations in the skin or the alleged metastatic tumors in the viscera are reticulum-cell sarcomas, but insist that the whole process is a specific granuloma. The extreme chronicity of some cases of classical mycosis fungoides, with a duration of from twenty to forty years, is held to be the strongest clinical argument against a malignant character.

Chancroid and the Emancipation of Women.—SPINDLER (*Arch. f. Derm. u. Syph.*, 1928, **154**, 292) reviews statistically the trend of incidence of the venereal infections before and since the World War, and compares it with the records of the source of infection in a series of cases covering the same periods. It appears that chancroid, for many years exceedingly common, is now rapidly on the decline as a veneral infection, while gonorrhea is proportionately on the increase. Coincidently it appears also that there has been a change in the sources of venereal infection. According to the studies of Paldrock, in the years of 1909 to 1918, 56 per cent of syphilitic persons in Dorpat were infected by professional prostitutes, while 52 per cent of gonorrheics and 60 per cent of persons with chancroid were infected from the same source. In the years 1921 to 1926 the proportion of chancroids of prostitute origin had risen to 77 per cent, and in the author's private practice to 92 per cent. The disease is five times as common in men as in women.

The author considers that the public prostitute is frequently an asymptomatic carrier of the Ducrey infection, and that she is the real reservoir of this particular venereal disease. He then proceeds to study the increase in the incidence of gonorrhea acquired from other than strictly prostitute sources, amounting to as high as 24 per cent since the World War. As a confirmation of the decreased influence of professional prostitution in the dissemination of venereal disease, he cites an almost complete disappearance of street-walking in Reval since 1918. The incidence of infection traceable to houses of prostitution has fallen in that city from 46 to 2 per cent. The author concludes from his examination of the figures, that the casual sexual activity of the industrially emancipated woman is responsible for the changes which are occurring; that with the transition from prostitution to promiscuity, chancroid, a disease of the dirty prostitute, will virtually disappear, while gonorrhea replaces it, and syphilis maintains an intermediate position. It appears, therefore, that the hope for an extinction of gonorrhea and syphilis by suppression of the prostitute reservoir is illusory.

On the Presence of the Cause of Herpes in Zosteriform Eruption and its Differential Importance.—FREUND (*Arch. f. Derm. u. Syph.*, 1928, **154**, 278) reviews the literature dealing with the finding of a virus capable of producing corneal reaction and encephalitic symptoms in rabbits, and points out that in true zoster, as distinguished from simple herpes, the presence of this virus cannot be demonstrated. He regards this as a sufficient demonstration of a fundamental difference between the two processes. He feels that it is, therefore, proper to speak of zoster-like lesions which clinically resemble herpes zoster, but in which no corneal reaction can be produced in the rabbit by the vesicle fluid, as zosteriform herpes. Herpes and zoster thus appear, in his opinion, to be separate conditions. There is a bibliography of thirty-five titles.

OBSTETRICS

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The Place of the Vaginal Cesarean Section in Obstetrics.—The more general adoption of the transperitoneal low abdominal Cesarean section has caused the literature of the last ten years to contain very little about vaginal Cesarean section. PHANEUF (*Am. J. Obst. and Gynec.*, 1928, **15**, 325), reporting a series of 27 cases, believes it has a very definite place in obstetrics when an indication for immediate delivery arises in

a gravida with a long, rigid, undilated cervix up to the end of the eighth month of gestation. The operation may be done at term, but here the difficulties are greater and there is danger of the incisions tearing into the peritoneal cavity because of the large size of the child. The operation is extraperitoneal, postoperative complications are negligible, the puerperium resembles that of any operative pelvic delivery and there is protection against infection to a greater extent than in low transperitoneal abdominal cervical Cesarean section.

The Heart in Pregnancy.—Functional changes in the normal heart during pregnancy are studied by GAMMELTOFT, of Copenhagen (*Surg., Gynec. and Obst.*, 1928, **46**, 382). Since there is hardly a single function of the maternal organism which is left unaffected by gestation, the question naturally arises, How does the circulatory system of the mother, especially the heart, react toward the new task? With this in view, they attempt to study the "normal heart in normal pregnancy," by making regular examinations throughout the entire period of pregnancy, puerperium and usually for some time afterward, by the usual methods of clinical examinations supplemented by the use of fluoroscopy and Roentgen ray plates, electrocardiography and in some cases a determination of the minute volume of the heart, that is, the amount of blood circulating through the heart in one minute. A total number of pregnant women studied was 327, but in only 239 cases were the studies completed; the patients were all primipara or Para II, between the ages of twenty and thirty-five years, of normal physique, weighing between 55 to 65 kg. and the height was 150 to 170 cm. The majority of these cases went through pregnancy and confinement without presenting any symptoms of a circulatory nature, nor did the usual clinical methods demonstrate any disturbance apart from a frequent accentuation of the pulmonary second sound during the last half of gestation and an occasional occurrence of extrasystoles and faint murmurs. More particular investigation showed that 39 out of the 239 perfectly healthy pregnant women presented some pronounced circulatory symptoms during the last half of gestation which suggested an organic heart lesion. Twenty-four out of 39 complained of dyspnea; the urine contained albumin in 19 cases; edema was present in 34 cases. Physical examination showed enlargement of the heart, rapid pulse, murmurs and accentuation of the pulmonary second sound. The blood pressure was practically always found normal. The chief complaints of these patients were cardiac pains and distress, headache and shortness of breath. It is characteristic that the lesion found was not aggravated by work nor was it improved by digitalis and rest in bed. In several instances the patients claimed to feel better while moving around. It was impossible during parturition to demonstrate any aggravation of the symptoms; these women were not exhausted, the respirations remained the same throughout and the blood pressure was normal. Practically all symptoms subsided before discharge from the hospital. Systematic Roentgen ray studies were made in 157 patients; of these, 118 cases had no cardiac disturbances whatever during the entire period of gestation, but in 23 cases there was an increase in the longitudinal diameter in 39 cases and transverse diameter in 33. This increase occurred before the time when the upward pressure on

the diaphragm could be of particular consequence. Examinations two to four weeks after parturition showed that both longitudinal and transverse diameters had returned to practically normal measures. In a series of 39 women suffering from a functional heart lesion the longitudinal and transverse diameters were enlarged in 21 and 22 cases respectively in the sixth and seventh month, and in 27 cases in the eighth to ninth month; these changes disappeared shortly after parturition. From the electrocardiographic studies in these cases the author considered that the left ventricle undergoes hypertrophy in the first six months of pregnancy and that the hypertrophy is compensated in the last months by a proportionate hypertrophy of the right ventricle. The functional hypertrophy of the two ventricles is disturbed in most cases of pregnancy, even the normal ones. There is perhaps also a slight dilatation of the right ventricle and right antrum. The investigations have shown that apparently normal and healthy women may during pregnancy develop symptoms which must be taken as a functional heart lesion, while they often, no doubt, have been considered organic heart disease.

GYNECOLOGY

UNDER THE CHARGE OF

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Radium in Cervical Cancer.—In the Philadelphia General Hospital Norris and Vogt (*Surg. Clin. of North America*, April, 1927, p. 315) group the cases of cancer of the cervix according to the classification of Schmitz, which means that Group 1 contains the cases in which the disease is apparently confined to the cervix. Group 2 are the cases of borderline operability. Group 3 are the clearly inoperable cases. Group 4 are the cases in the terminal stages of the disease. Group 5 represents references following attempts at radical removal. They believe that in the first group irradiation and radical hysterectomy produce practically equivalent results. In all other cases, however, irradiation is definitely superior, not only as a palliative but as a curative measure. In cases in the first group 2400 mc. hours of radium are applied to the cervix, either in the form of element or properly screened emanation. In many instances a high amputation of the cervix is performed with the cautery and followed immediately by irradiation of the cervical stump. The bladder and rectum are kept out of harm's way by means of gauze packing. A second application of similar dosage is often used two or four weeks later, and in some instances a third or even a fourth application may be indicated, depending upon the local and general

reaction. The cases in Group 2 are treated practically the same as those in Group 1. In Group 3 the ultimate prognosis is generally unfavorable, but a few cases may be permanently cured and much benefit can generally be secured so far as the local lesion is concerned. Hemorrhage and discharge can usually be checked, and as a result the symptoms incident to the former disappear, cellulitis of the broad ligaments is alleviated and improvement in the general health occurs. Such patients are frequently able to resume their former life despite the fact that the deeper portions of the tumor may still be developing. They were able to secure complete local healing in 70 per cent of all the cases. The cases in Group 4 are rarely amenable to any form of irradiation therapy, since attempts at irradiation are prone to aggravate the lesion and result in a high percentage of vesical or rectal fistulæ. It is only the exceptional case of this group that receives any irradiation in their clinic. The cases in Group 5, they believe, are best treated by means of bare tubes. Carcinoma of the cervical stump following supravaginal hysterectomy is usually treated by the insertion of 50 to 100 mg. of radium for eighteen to twenty-four hours. When a second irradiation is to be used bare tubes or radium-bearing needles are applied to the lesion for a distance of 1 cm. beyond the edge of the carcinoma. They routinely employ deep Roentgen ray therapy in all cases of cervical cancer in which any hope whatever is present of an ultimate cure. Early in the history of radium therapy it was discovered that certain tumors responded more favorably to its influence than did others. As a general rule, the more embryonal the type of tumor the more favorable does the tumor respond to adequate irradiation. On the other hand, the embryonal tumors are, as a rule, the more malignant, exhibit more rapid growth and produce the earlier metastasis. However, a careful study of end results fails to show any material difference in the five-year salvage in the different types of tumors. The greater malignancy and the earlier metastasis developing in the embryonal forms probably counterbalance their greater susceptibility to irradiation. The more embryonal types of tumors grow more rapidly and hence are likely to be more advanced when first observed. As a general rule, the papillary form reacts more favorably to treatment than the ulcerative or interstitial types. The cases observed in the Philadelphia General Hospital were nearly all in Groups 3, 4 and 5. This is the sad experience which all of us have, so that we should be very grateful that we have such an agent as radium, which at least will give some little comfort to the unfortunate possessors of these distressing tumors.

Histologic Malignancy Index in Relation to Prognosis.—For several years the attention of many cancer students has been turned to the question of the relation of the degree of histologic malignancy of a growth to the prognosis following treatment. Many methods have been devised to determine this malignancy index, but the results of most of these methods are quite parallel. SCHMITZ (*Radiology*, 1927 **9**, 322) has devised a method of his own and in considering this question in relation to the subject of cervical cancer, his experience leads him to believe that Roentgen rays and radium applied to these growths should be used according to strict indications which should be based on the clinical grouping and the histologic malignancy index. Carcinomata

which offer a poor prognosis as determined by these methods should not be treated with irradiation. Carcinomata of all other groups and grades give every hope of being arrested by the combined application of Roentgen rays and radium. However, the more extended the disease is and the higher the malignancy index rises, the fewer are the good end results obtained. It is important for all of us to bear this idea in mind. We have known, of course, for some time that all cervical cancers do not react the same to irradiation, some being much worse after treatment. If we can tell beforehand which cases will be made worse, as the author claims, we shall be able to save some patients from unnecessary treatments, discomfort and expense and still feel that no helpful treatment has been neglected.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Nature of Progressive Deafness: Further Studies.—Believing that progressive deafness is not a distinct entity, that in most instances progressive deafness is a local manifestation of a general metabolic disorder, and that the present classification of deafness is a hindrance to investigation and research in that it offers both a hypothesis and a conclusion, KOPETZKY (*Arch. Otolaryngol.*, 1927, **5**, 404) employs the term *progressive deafness* to signify any deafness that is progressively getting worse and, consequently, one which embraces all types of deafness as they are ordinarily classified. The older classification of deafness into two groups—conduction and perceptive—is discarded for one based on audiometric determinations. This latter is composed of four basic types of curves—the straight line, the diagonal down in the low tones, the diagonal down in the high tones and the curve down on both ends. It was found that the respective clinical diagnoses (conduction, perception, otosclerosis) do not correspond, generally, with any one of these curves. In other words, progressive deafness does not necessarily give a definite type of hearing curve. Therefore, it is impossible to recognize or diagnose a progressive deafness from the hearing tests alone. For the purpose of study, all cases were divided into acute or chronic, and the latter into progressive or nonprogressive. Sixty-three persons were examined intensively. After a complete history a thorough investigation of the oto-rhino-laryngologic apparatus was made; chemical and serologic studies of the blood were conducted, and a general survey by an internist was done. Eighty-eight per cent of the patients said that their deafness was progressive; 60 per cent gave a definite history of deafness in other blood relatives; all had a raised lower tone limit and increased tone conduction; 40 per cent were examined by an internist, all of which showed a chronic metabolic disease elsewhere in

the body; 100 per cent yielded a disturbed calcium metabolism, 84 per cent being decreased and 16 per cent increased; 76 per cent exhibited an increase in the blood uric acid. From his observations, the author believes that chronic progressive deafness is a local manifestation of a general metabolic disorder, being confident that it rarely, if ever, exists as an isolated entity. Further studies on the calcium content of the blood in cases of deafness have made him certain of the value of the derangement of this element in establishing a diagnosis of chronic progressive deafness.

The Histopathology of the Tonsil in Acute Rheumatic Fever and Chorea.—Stimulated by the knowledge of the wide dissemination of a distinctive lesion of rheumatic fever throughout the human body and the experimental animal; cognizant of the failure to find similar morphologic responses in the lymphoid elements of the tonsil; aware of the well-known association of tonsillitis and rheumatic fever, MACLACHLAN and RICHEY (*Trans. Assn. Am. Phys.*, 1927, **42**, 315) examined, microscopically, the tonsils which had been removed from a series of clear-cut, unquestioned cases of acute rheumatic fever and chorea, paying especial attention to the capsular and pericapsular tissues of the tonsils. In 18 cases of rheumatic fever and 5 of chorea a study of the capsular and pericapsular tonsillar tissues showed, in 14 of the former and 4 of the latter, perivascular lesions consisting of lymphoid and plasma cells (78 per cent). In addition, such findings as atrophic muscle giant cells, fibrosis, bone and cartilage, and foreign-body giant cells in the stroma of the mucous glands were encountered. An endothelial proliferative reaction of the lining cells of the capillaries and perivascular lymph spaces was noted in 11 cases (48 per cent). Some of the endothelial cells were multinucleated and were associated with granulomatous-like lesions in 6 instances (26 per cent). The endothelial cell response was the outstanding feature in this study. The authors are not prepared at this time to state that it is a specific reaction for rheumatic fever or chorea. In general, a comparison of the clinical data with the pathologic findings revealed that the more severely acute and the more prolonged recurrent cases exhibited the most distinctive lesions.

RADIOLOGY

UNDER THE CHARGE OF

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Anatomic and Postural Variations of the Normal Spine.—Sacralization of the fifth lumbar vertebra is not a pathologic or traumatic lesion, according to SKINNER (*Radiology*, 1927, **9**, 451), but is an anatomic

variation of the normal. Spina bifida occulta, or failure of the neural arch to close, is neither traumatic nor pathologic. It is a variation in anatomic development without symptoms. Postural variations of the lumbar spine should not always be considered pathologic. Age changes in the spine, sometimes described as osteoarthritis, or hypertrophic arthritis with gross spur formations, are not necessarily pathologic. They are often the response of the spine to the stress and strain of natural or occupational demands, and are not invariably the result of infection or trauma. Separate centers of ossification without fusion, on one or both sides, may occur at the transverse process of any lumbar vertebra, usually the first. By some these shadows are interpreted as supernumerary ribs. They are frequently misinterpreted as fractures. It should be understood thoroughly that these transverse processes are excellently guarded by cushions of muscle and massive ligaments. They are broken by extreme direct violence, as by hammers, horseshoes and so forth, but are rarely broken by muscle strain, spinal wrenching, bending or bruising.

Concentration of Cholecystographic Mediums and Bilirubin by the Gall Bladder.—The shadow obtained by cholecystography is the result of concentration of the opaque medium in the bile by the liver, and it would appear reasonable that the concentration of the medium, and hence the density of the shadow, would parallel the concentration of the bile pigment by the gall bladder. However, studies by KIRKLIN, CAYLOR and BOLLMAN (*Radiology*, 1927, **9**, 463) indicate that no such constant parallelism exists. One hundred and thirteen cases, covering various types of cholecystic disease, were studied. The group of cases in which there was a bilirubin content of less than 10 mg. for each 100 cc. of gall bladder bile did not have a shadow of the gall bladder in the roentgenograms, and parallelism thus obtained in this group. In the intermediate group with a bilirubin content of 11 to 50 mg., which is about the normal variation, there was no constant relation between the cholecystographic shadow and the bilirubin content. In the third group, with a bile pigment content of more than 50 mg., the writers were surprised to find that the cholecystographic compound rarely produced a shadow, and this was possibly because the bile was already concentrated to its maximum.

Possible Developmental Defects following Overradiation of the Thymus in Early Infancy.—HESS (*Radiology*, 1927, **9**, 507) adduces authority for the statement that the Roentgen ray has an intense effect on the thymus, manifesting itself in degeneration, especially of the lymphocytes. Regeneration may occur, but the gland can be completely destroyed by heavy dosage. The author reports the cases of 2 children, both of whom were treated four years ago for enlargement of the thymus with the Roentgen ray in heavy dosage. Both of the children, 1 of whom died subsequently, developed the physical and mental features of Mongolian idiocy and never learned to walk or talk. The writer realizes that 2 cases offer little to support the theory that a hypothymic condition results from heavy radiation, but he suggests that these cases should be treated with small doses, repeating only when necessary to relieve symptoms.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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A Study of the Endocrine Organs in the Psychoses.—LEVIN (*Am. J. Psychiat.*, 1927, **7**, 391) presents a valuable and timely study of his own findings regarding the histopathology of the endocrine organs of all psychotic cases coming to necropsy in the W. G. State Hospitals within six hours after death. The organs examined were the hypophysis, the thyroid gland, the adrenal glands and the sex glands. Clinical reports were not available until after the material had been studied and the findings recorded precluding clinical bias. For the details of analysis the reader is referred to the original article, which is too extensive for reproduction here. The most interesting result is that the author finds no substantiation of the theories of Mott, Lewis and others, that specific changes in various endocrine organs are found in dementia præcox. The pathologic changes found in the various organs showed little difference in the various psychotic groups, and seemed to be correlated with tuberculosis, syphilis, acute infections and so forth, rather than with the type of psychotic manifestation. He emphasizes that he does not mean to assert the absence of any possible relation between endocrine organs and psychosis in those groups, such as dementia præcox, where his findings were essentially negative. Analyzing prævious material reported for the dementia precox group, the author is able to show that his material was quite comparable to the material on which several untenable hypotheses have been based.

The Need for Coöperation between the Legal Profession and the Psychiatrist in Dealing with the Crime Problem.—WHITE (*Am. J. Psychiat.*, 1927, **7**, 493) states that the psychiatrist has come to feel that the criminal law and methods of legal procedure are largely obsolete from his point of view, and that present penal methods are inadequate. He considers that criminal law and practice are based upon the ideas of punishment and vengeance rather than upon any attempt to comprehend the problem of the individual involved. In place of this the law has assumed a hypothetical individual, "the man in the street" or "the average man." Moreover, the procedure is limited to three solutions—death, imprisonment or fine. He sees an attempt being made toward this goal in the fact that the American Bar Association set aside a session to be devoted to psychiatry (before which the paper was read). Socially, the evolution of the juvenile court with its casting aside of the traditional approach in seeking in each case to find the proper solution, indicates a pattern along which the new development may take place. The author makes the following suggestions: (1) Society has the right to segregate the dangerous antisocial types as

long as they continue dangerous. This means largely doing away with fixed sentences, at least for certain types of crime, and making the return to freedom conditional upon some change in the individual that gives one a right to suppose that perhaps he will function more effectively as a social unit than he has in the past. (2) The elimination of punishment as a vengeance motive and its retention only if used for definitely constructive ends for conditioning conduct. (3) The gradual transformation of prisons into laboratories for the study of human behavior and the conditioning of human conduct. (4) The abolition in the trial of the hypothetical question. (5) The discarding of the concept of responsibility. (6) The making of the positions of district attorney and of judges of criminal courts permanent positions and the appointment thereto a result of competitive examination protected by civil service laws. The requirements for filling such positions should be a knowledge of modern criminology in its various ramifications. (7) To have such district attorneys and such judges in the course of their educational preparation serve internships in psychiatric clinics and prisons. The author feels that the present system is an anachronism that is rapidly being outgrown, and believes that psychiatry has much to offer in developing more adequate procedures.

Epileptic Variants.—Wilson (*J. Neurol. and Psychopath.*, 1928, **8**, 223) considers as the physiologic basis for epilepsy an escape from physiologic inhibitions. "Whether they indicate only 'release' or also 'irritation' is immaterial or at least of secondary importance." In connection with these phenomena of escape from inhibitions, he believes there are often symptoms of a psychic and a sensory order as well as of the motor order. He would, therefore, consider as epileptic variants those cases in which psychic or sensory phenomena show a typical release characteristic whether or not they are accompanied by motor phenomena. He objects to the term "epileptic equivalents" for such manifestations. On the same basis he thinks that we might distinguish frontal, Rolandic, parietal, occipital, temporal, mesencephalic, pontine, bulbar and cerebellar epilepsies. He thinks there may also be spinal varieties and possibly varieties affecting visceral-neural plexuses and ganglionic collections. As motor variants he lists myoclonic or regional epilepsy, epilepsia partialis continua, tonic epilepsy, coördinated epilepsy and inhibitory or akinetic epilepsy. As sensory variants he mentions reflex epilepsy, sensory epilepsy and affective epilepsy. As psychic variants he would place those psychic phenomena formerly considered as psychic equivalents, especially the preconvulsive and postconvulsive states when they occur without convulsion or spasm. He cites cases to illustrate each of these types and calls attention to the escape of function characteristic of each. He discusses at some length visceral variants which he considers to include especially vasovagal attacks. These include attacks referring to the cardiorespiratory system, the gastrointestinal system and the genitourinary system which are generally accompanied by vasomotor symptoms and psychic symptoms of sensations of impending catastrophy. Among other visceral fits he cites two cases of paroxysmal yawning attacks, one of which is accompanied by headache and vomiting. The other is accompanied by voiding of urine and followed by giddiness, headaches and occasional vomiting.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Bacterial Allergy in Infection.—The view that certain infectious diseases are based on allergic reactions has not been supported by very much experimental evidence. ZINSSER and GRINNELL (*J. Bact.*, 1927, **14**, 301) have studied the problem of pneumococcus allergy and were able to obtain allergic reactions often more severe than those found in the most extreme tuberculin reactions. A temporary concentration of the antigen, such as occurs in the skin tests, seemed necessary, since intraperitoneal injections of antigen gave but slight reactions. The kind of antigen used was the determining factor. They noted that normal guinea pigs gave occasional severe skin reactions to pneumococcus preparations, and discovered that these reactions were related to the age of the animals and suggested their origin in spontaneous sensitization. They were able to hypersensitize guinea pigs by autolysates often very rapidly (five to seven days with daily injections) and also to desensitize them, but these results were very much less striking when whole bacteria were used. They believed the autolysate (which is heat stable) more nearly represents the antigen liberated in the body during infection than does any other *in vitro* product. Bile solutions of pneumococci were found to give comparable results to those obtained with the autolysates and these two preparations were considered antigenically equivalent, and they support the view of ATKIN (*Brit. J. Exp. Path.*, 1926, **7**, 167), that the bile solution represented a speeding up of the autolysis. The sensitization was found to be group but not type specific. Sera from sensitive or highly immunized animals were found to have only a slight neutralizing effect on the antigen and attempts at passive sensitization were negative. The suggestion is made that these results may have some bearing upon the occurrences in human pneumonias and that sensitization may take place during the course of the infection.

Pulmonary Sporotrichosis.—FORBUS (*Am. Rev. Tuberc.*, 1927, **16**, 599) reports the results of the study of a case of pulmonary sporotrichosis together with a review of those cases previously recorded. Nine such cases have been reported; after a critical examination of these the author comes to the conclusion that in only 1 case, that of Warfield, in 1922, is there satisfactory evidence of a pulmonary lesion due to the sporotrichum. Although over 400 cases of all types of sporotrichosis have been reported, only 1 case with pulmonary localization is satisfactorily substantiated. It is, therefore, evident that pulmonary infections, and indeed visceral lesions of any kind, are extremely

rare. In the author's case the lesions, though most probably due to infection by sporotrichum, were found in the lungs and spleen. They appeared somewhat similar to those produced by the tubercle bacillus, but are by no means identical with them. The fungus was obtained by culture from the lungs, but no attempt was made to make cultures from the spleen. Animal inoculations were negative. The septicemic nature of many apparently localized sporotrichum infections and the lack of visceral lesions in such cases is commented upon. It is pointed out that because of the rarity of visceral lesions in sporotrichum infections little attention need be paid to the probability of their occurrence in the differential diagnosis of obscure pulmonary conditions.

Scarlet Fever Streptococci in Throats of Diphtheria Patients.—The frequent association of streptococci in diphtheria has long been known, and the view has been that these streptococci often added to the severity of the infection. Since the methods for the recognition of the scarlatinal streptococci have been available little work has been done to determine the incidence of hemolytic streptococci in diphtheria. RHOADS (*J. Infect. Dis.*, 1927, **41**, 377) has studied this problem, and he found hemolytic streptococci in the throats of 29 from 100 cases diagnosed diphtheria. Sixteen of these were identified as scarlatinal strains. The Dick test was done on 24 of these 29 cases and 7 (24.1 per cent) gave positive results while the streptococci from 6 of these 7 produced practically no, and the other strain only a very weak, toxin. The Dick test was also positive in 33 of 68 patients without hemolytic streptococci in their throats (48.5 per cent). Three patients in his series showed a combination of scarlet fever and diphtheria, and he suggested that scarlet fever may be diagnosed as diphtheria because of positive cultures.

Vaccination of Animals against Anthrax with Edema Fluid.—Anthrax vaccination in the history of bacteriology has always been of interest largely because of its wide application. HRUSKA (*Ann. de l'Inst. Pasteur*, 1926, **40**, 710) stimulated by Besredka's method of cutaneous vaccination undertook to vaccinate guinea pigs with products of Bacillus anthracis other than the previously used first and second vaccine cultures. He used a variety of materials—filtrates of cultures, extracts of organs of anthrax animals, and the edema fluid from anthrax guinea pigs and rabbits sterilized by heat or formalin. He found that only the latter, that is, the formalin-treated edema fluid, would vaccinate guinea pigs by intracutaneous injection against virulent Bacillus anthracis, but this immunity was not transmissible to fresh guinea pigs through the defibrinated blood of the immune pig. URBAIN and ROSSI (*Compt. rend Soc. de biol.*, 1926, **95**, 544; 1927, **97**, 599) used edema fluid treated with chloropicrin and were successful in immunizing half their guinea pigs after subcutaneous or intraperitoneal injections and all when they used the intracutaneous or cutaneous method. The technique they believed explained Bail's difficulty in immunizing guinea pigs with the "aggressins" of edema fluids. They further found in immunizing rabbits that the skin vaccination gave a stronger and more permanent immunity than subcutaneous injections.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Milk-borne Epidemic of Poliomyelitis.—AYCOCK (*Am. J. Hyg.*, 1927, **7**, 791) reports an epidemic of poliomyelitis of unusual severity and presenting features not generally encountered in outbreaks of this disease, which occurred in Broadstairs, England, a city of 15,471 population, in October, 1926. This outbreak started and subsided suddenly, 62 cases being reported between October 14 and 29; 31 of them on October 14 and the five days following. There were 75 cases in all. Other outstanding features were that multiple cases occurred in private boarding schools having little communication with the town or with each other, and that only the well-to-do class of the population was affected. The epidemic was confined strictly to Broadstairs. In addition, 3 visitors who had left Broadstairs just previous to the outbreak developed the disease during the epidemic. The distribution of cases, in point of time, indicates that the majority were simultaneously infected. The data concerning the 4 cases who left Broadstairs before the epidemic fixes with a high degree of probability a definite period of infection, from which it may be inferred that the incubation period was in the majority of cases between six and fourteen days. There was clear epidemiological relationship with a particular milk supply, 50 cases occurring among known users of this milk and 19 others in individuals supplied by another dealer who was known to have purchased a part of the suspected supply.

Ultraviolet Light and Vaccine Virus: I. The Reaction of Irradiated Skin to Vaccine Virus.—RIVERS, STEVENS and GATES (*J. Exper. Med.*, 1927, **47**, 37) found that rabbit skin treated for a few minutes with ultraviolet light and then inoculated at once with vaccine virus is less susceptible to the action of the virus than is untreated skin. If twenty-four, forty-eight or seventy-two hours elapse between the time of irradiation and inoculation the treated skin appears to be more susceptible than is untreated skin. Skin repeatedly exposed to ultraviolet light is less susceptible to the action of vaccine virus than is nonirradiated skin.

II. The Effect of Monochromatic Ultraviolet Light upon Vaccine Virus.—RIVERS and GATES (*Ibid.*, p. 45) found that under the experimental conditions which they describe the amount of energy required to kill staphylococci at single wave lengths in the active ultraviolet region was approximately the same as that necessary to inactivate vaccine virus.

A Study of the Pellagra-preventive Action of the Tomato, Carrot and Rutabaga Turnip.—GOLDBERGER and WHEELER (*Pub. Health Repts.*, 1927, **42**, 1299), by means of feeding experiments on inmates of a state sanitarium, showed that milk, meat, yeast and certain other materials had valuable pellagra-preventing properties. This is due to a factor designated "P–P" (pellagra-preventive) which probably is identical with the growth-promoting element which has been included in the water-soluble B vitamin, also sometimes called the antineuritic vitamin. The summary and conclusions of the present work are as follows: The expressed juice of canned tomatoes given in a daily quantity of approximately 1200 gm. (40 ounces) was found to possess well-marked pellagra-preventive action. A daily supplement of cooked carrots equal to 453 gm. (1 pound) of the dressed, raw vegetable failed as a pellagra preventive. A daily supplement of cooked rutabagas equal to 453 gm. (1 pound) of the dressed, raw vegetable failed as a pellagra preventive. The failure of the carrots and of the rutabagas may have been due to the ingestion of a quantity which, although seemingly liberal, was too small; nevertheless, if carrots and rutabagas, as is probable, actually possess pellagra-preventive action, this must be rather feeble. Although definitely demonstrated, the pellagra-preventive potency of canned tomatoes must be rated as of a feeble order. Tomatoes are recommended for use in the treatment of active cases of pellagra, and it is suggested that a more liberal use of this vegetable, particularly in the late winter and spring, be encouraged as a preventive measure.

Viability of Pathogenic Organisms in Butter.—BERRY (*J. Prev. Med.* 1927, **1**, 429) has demonstrated that butter cannot be disregarded as a potential factor in the spread of communicable diseases. The barriers generally regarded as sufficient protection—acidity and salt content—may be either absent or present in such small quantities as to play a negligible part. The viability of pathogenic organisms in butter seems to be dependent upon their ability to survive in unnatural conditions where there is neither temperature nor food suitable for growth and multiplication. The resistance of typhoid organisms in butter for at least three and a half months creates a public health menace where butter is improperly cared for, while the organisms commonly associated with food infections are even more resistant and able to survive for a period—seven and a half months—equal to or greater than the time that butter would be kept under commercial conditions. In view of this, the question might well be considered as to whether numerous cases both of typhoid and related diseases of untraceable origin do not in part arise from infected butter.

Shellfish Sanitation.— FISHER (*U. S. Pub. Health Repts.*, 1927, **42** 2291) says that the first observation of the relation of contaminated shellfish to typhoid fever was in 1816 by Pasquier, a French physician. An incomplete list shows twenty-six epidemics, chiefly typhoid fever. There were two epidemics of cholera. The relatively recent epidemic of New York, Chicago and elsewhere focused attention on the importance of the problem and led to present measures looking to the safeguarding of the public health, and, indeed, of the industry. Each

state exercises supervision over shellfish production and handling within its own borders and issues certificates to producers whose products are regarded as safe.

Cases of Nontuberculous Granulomatous Lymphadenitis in Mississippi.—BARBER and COOGLE (*Pub. Health Repts.*, 1927, **42**, 1306) state that the onset suggests an acute infectious disease with headache, fever and chills. There may be pain and tenderness in the groin. This is followed by an inguinocrural tumor involving one or more lymph nodes and often going on to suppuration. The prognosis is good. Laboratory tests are all negative. The portal of entry is unknown, though there is a suggestion that it is to be found in relation to the sexual organs in some cases. A small epidemic is described, though without any evidence of association between cases.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 16, 1928

Optical Rotation of Pseudomorphin.—A. K. BALLS and W. A. WOLFF (from the Laboratory of Pharmacology, University of Pennsylvania). The optical rotation of pseudomorphin dissolved in KOH solutions varies directly as pseudomorphin concentration with constant alkali, and inversely as alkali concentration with constant pseudomorphin. But except when the solutions are apparently supersaturated with a potassium pseudomorphin compound the observed rotation (as defined below) is constant for any given ratio of alkaloid to [OH], irrespective of the concentration of alkaloid. The rotation decreases with increase in the ratio $(f(a)/c$, where f is the mean activity coefficient of KOH at the molar concentration a, and c is the molar concentration of pseudomorphin. The data fit the empirical equation $M\left(\frac{f(a)}{c}+10\right)^{0.435}=572$ where $M=\frac{\text{observed rotation for 1 decim. (D light)}}{c}=0.568\ [\alpha]_D$, thus calculating the data to a molecular basis, neglecting the specific gravity of the solution. By extrapolation Mo, the highest possible rotation = 210 units as above. Hence, the equation (still empiric) becomes $\frac{M}{Mo}\left(\frac{f(a)}{c}+10\right)^{\log_{10}e}=c$, which may possibly have more general application. Agreement between this formula and observed readings is extraordinarily close over the entire range of concentrations suitable for observation. Crowding the particles of the solution, by supersaturation, addition of KCl, or of large excess of KOH, causes the rotation to approach Mo. This, as well as the above formula, is difficult to explain by the usual applications of the dissociation theory.

A jelly-like compound of K and pseudomorphin may be separated from supersaturated solutions, but is stable only in strong KOH. Analyses of the supernatant liquid indicate a withdrawl of H_2O from the solution. This complicates any attempt to define the reaction and points to colloidal behavior. On heating the solution the gel becomes crystalline and then corresponds to a monopotassium pseudomorphinate, under the unproved assumption that in this case no H_2O is withdrawn from the solution.

Change in the Reaction of the Skin to Histamine as Evidence for Deficient Circulation in the Lower Extremities.—Isaac Starr, Jr. (from the Laboratory of Pharmacology, University of Pennsylvania). When a minute amount of histamine is pricked into the skin a wheal surrounded by a flare is produced. Sir Thomas Lewis has demonstrated that when the circulation is mechanically obstructed or diminished by cold this reaction is delayed, altered or abolished. This suggested that the reaction of the skin to histamine might be used as a test for deficient circulation in the extremities. Fifty tests on normals or patients with normal circulations showed that the reaction appeared within two and a half minutes and both wheal and flare were present within five minutes. The reactions from thigh to foot were approximately equal. In twenty-five tests on patients with strong clinical evidence of circulatory impairment in the feet, the reaction on the feet was markedly delayed and reduced, and in certain instances the wheal or flare, or both, failed to appear. In the majority of these cases the reaction above the knee was normal. Certain cases of diabetes with negative physical examinations showed delayed reactions to histamine on the feet. Determinations of "blood flow" by the Stewart calorimeter gave abnormally low results in these cases. Reactions similar to those seen in pathologic conditions were produced in normals by partly obstructing their circulations mechanically or reducing the blood flow by exposure to cold, confirming Lewis' experiments. We, therefore, conclude that the appearance time and intensity of the reaction to histamine varies with the circulation and so may be used as a test for circulatory deficiency. It is hoped that this test will make the diagnosis possible before the development of physical signs, give confirmatory evidence after these have developed and aid in determining the level of amputation.

Distribution of Antibodies in the Serum and Organs of Rabbits.—Jules Freund and Caroline E. Whitney (from the Henry Phipps Institute of the University of Pennsylvania). In passively immunized rabbits the accumulation of agglutinins is completed within fifteen minutes after the injection of immune serum in the liver, spleen, kidney, lung, whereas it continues for several hours in the brain, uterus, muscles of the leg and skin. Perfusion of the living animal reduces the agglutinin content of the liver and spleen parallel with the reduction that occurs in the titer of blood serum. The agglutinins of uterus or skin are not removed by perfusion. There is some parallelism between the rate of accumulation and also the final amount of agglutinins in the organs and the lymph of the organs. The rate of accumulation and also the final amount of agglutinins is higher in the lymph of liver than

in the lymph of leg and higher in the liver tissue than in the muscle and subcutaneous tissue of the leg. Agglutinins injected into the dermis do not become fixed permanently at the site of injection but about ten days must elapse until they are distributed throughout the body. These observations may throw light upon the mechanism of systemic and local anaphylaxis.

The Structure of Medullated Nerve Fibers of the Frog.—GEORGE ST. DE RENYI (from the Department of Anatomy, University of Pennsylvania). Living nerve fibers of the frog, some of which had been previously treated with silver nitrate, vital dyes and various fixatives, were dissected under the high-power microscope. These experiments yielded the following results: The connective-tissue sheath around the single fibers (sheath of Henle) was found to consist of a framework of very delicate fibers and a sticky, mucous-like substance. The physical state of the axis cylinder appeared as a soft gel, with elastic and plastic features. The substance of the nodes was found to be more viscous or solid. The neurolemma was seen to form a continuous membrane. The axolemma, described by some authors, does not seem to exist at all. No organic connection could be shown between neurolemma on one side and myelin on the other, although some delicate fibers, or bridges, do exist between the myelin sheath and the axis cylinder, representing a connection between the two structures. True silver-nitrate impregnation is obtained only in the case of the node. The internodes, even after removal of the myelin sheath which covers them, never stained as deeply as the nodes. The typical figures of the crosses of Ranvier were found to be due to the impregnated nodes with the addition of dark granules, which were very probably precipitated on the outer side of the neurolemma.

Correction.

In the article by Drs. Nye, Zerfas and Cornwell in the February number of the *Journal*, in Table I the first three full pages concern strains of yeast-like fungi obtained from stools. Under the column heading "Colonies obtained" on pages 158 and 160 delete the words "Stools" and transpose the subheadings, "Stool" and "G.C."

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